L43 0 S L37 NOT L9
L44 110 DUP REM L25 (73 DUPLICATES REMOVED)
L45 10 FILE MEDLINE
L46 8 FILE BIOSIS
L47 11 FILE CA
L48 6 FILE WPIDS
L49 0 FILE JICST-EPLUS
TOTAL FOR ALL FILES
L50 35 S L25 AND STABL?
L51 20 DUP REM L50 (15 DUPLICATES REMOVED)

=> d his

(FILE 'HOME' ENTERED AT 16:02:23 ON 03 MAY 1997)

FILE 'MEDLINE, BIOSIS, CA, WPIDS, JICST-EPLUS' ENTERED AT 16:02:55
ON 03 MAY 1997
L1 2514 FILE MEDLINE
L2 3034 FILE BIOSIS
L3 2344 FILE CA
L4 151 FILE WPIDS
L5 494 FILE JICST-EPLUS
TOTAL FOR ALL FILES
L6 8537 S (IFN OR INTERFERON) (W) BETA
L7 6911 FILE MEDLINE
L8 12731 FILE BIOSIS
L9 29241 FILE CA
L10 4914 FILE WPIDS
L11 927 FILE JICST-EPLUS
TOTAL FOR ALL FILES
L12 54724 S (LOW PH) OR (PH (3A) (3.0 OR 4.0))
L13 1 FILE MEDLINE
L14 3 FILE BIOSIS
L15 8 FILE CA
L16 3 FILE WPIDS
L17 0 FILE JICST-EPLUS
TOTAL FOR ALL FILES
L18 15 S L6 AND L12
L19 11 DUP REM L18 (4 DUPLICATES REMOVED)
L20 45 FILE MEDLINE
L21 48 FILE BIOSIS
L22 68 FILE CA
L23 22 FILE WPIDS
L24 0 FILE JICST-EPLUS
TOTAL FOR ALL FILES
L25 183 S (IFN OR INTERFERON) AND L12
L26 0 FILE MEDLINE
L27 0 FILE BIOSIS
L28 1 FILE CA
L29 0 FILE WPIDS
L30 0 FILE JICST-EPLUS
TOTAL FOR ALL FILES
L31 1 S L25 AND MANNITOL AND ALBUMIN
L32 0 FILE MEDLINE
L33 1 FILE BIOSIS

L34 6 FILE CA
L35 2 FILE WPIDS
L36 0 FILE JICST-EPLUS
TOTAL FOR ALL FILES
L37 9 S L25 AND (MANNITOL OR ALBUMIN)
L38 0 FILE MEDLINE
L39 0 FILE BIOSIS
L40 0 FILE CA
L41 0 FILE WPIDS
L42 0 FILE JICST-EPLUS
TOTAL FOR ALL FILES
L43 0 S L37 NOT L9
L44 110 DUP REM L25 (73 DUPLICATES REMOVED)
L45 10 FILE MEDLINE
L46 8 FILE BIOSIS
L47 11 FILE CA
L48 6 FILE WPIDS
L49 0 FILE JICST-EPLUS
TOTAL FOR ALL FILES
L50 35 S L25 AND STABL?
L51 20 DUP REM L50 (15 DUPLICATES REMOVED)

=> s l6 and (mannitol and albumin)
L52 0 FILE MEDLINE
L53 0 FILE BIOSIS
L54 7 FILE CA
L55 5 FILE WPIDS
L56 0 FILE JICST-EPLUS

TOTAL FOR ALL FILES
L57 12 L6 AND (MANNITOL AND ALBUMIN)

=> dup rem l57
PROCESSING COMPLETED FOR L57
L58 9 DUP REM L57 (3 DUPLICATES REMOVED)

FILE 'USPAT' ENTERED AT 11:37:04 ON 03 MAY 1997 * * * * * * *
* *
* W E L C O M E T O T H E *
* U. S. P A T E N T T E X T F I L E *
* *
=> s interferon? (p) (composition (p) (mannitol (p) albumin (p) acetate))
4113 INTERFERON?
398520 COMPOSITION
19192 MANNITOL
22089 ALBUMIN
199444 ACETATE
L1 0 INTERFERON? (P) (COMPOSITION (P) (MANNITOL (P) ALBUMIN (P)
AC
ETATE))
=> s (Ifn or interferon) (3a) beta
929 IFN
3535 INTERFERON
152792 BETA
L2 838 (IFN OR INTERFERON) (3A) BETA
=> s l2 (p) (stable (5a) (formulation or preparation or composition))
293289 STABLE
99163 FORMULATION
335342 PREPARATION
398520 COMPOSITION
L3 11 L2 (P) (STABLE (5A) (FORMULATION OR PREPARATION OR COMPOSIT
ION
))
=> d 1-11
1. 5,431,909, Jul. 11, 1995, Stabilization of human interferon; William E. Stewart, II, 424/85.4, 85.5, 85.6, 85.7; 530/351 [IMAGE AVAILABLE]
2. 5,425,940, Jun. 20, 1995, Combination therapy using interleukin-2 and tumor necrosis factor; Robert Zimmerman, et al., 424/85.1, 85.2; 514/2, 8 [IMAGE AVAILABLE]
3. 5,183,746, Feb. 2, 1993, Formulation processes for pharmaceutical compositions of recombinant .beta.-; Ze'Ev Shaked, et al., 435/69.51; 424/85.6; 530/351 [IMAGE AVAILABLE]
4. 5,098,702, Mar. 24, 1992, Combination therapy using interleukin-2 and tumor necrosis factor; Robert Zimmerman, et al., 424/85.1, 85.2; 514/2, 8 [IMAGE AVAILABLE]
5. 5,004,605, Apr. 2, 1991, Low pH pharmaceutical compositions of recombinant .beta.-interferon; Susan Hershenson, et al., 424/85.6; 530/351 [IMAGE AVAILABLE]
6. 4,992,271, Feb. 12, 1991, Formulation for lipophilic IL-2 proteins; Wolfgang H. Hanisch, et al., 424/85.2, 85.1, 85.4, 85.5, 85.6, 85.7; 435/811; 514/2, 8, 12, 21, 885, 970; 530/351 [IMAGE AVAILABLE]
7. 4,961,969, Oct. 9, 1990, Process for recovering microbially produced interferon-.beta.; Susan Hershenson, et al., 435/69.51; 424/85.6; 530/351 [IMAGE AVAILABLE]
8. 4,863,727, Sep. 5, 1989, Combination therapy using interleukin-2 and tumor necrosis factor; Robert Zimmerman, et al., 424/85.2; 435/69.5, 69.52; 514/2, 8 [IMAGE AVAILABLE]
9. 4,816,440, Mar. 28, 1989, Stable formulation of biologically active proteins for parenteral injection; James W. Thomson, 514/12; 424/85.6 [IMAGE AVAILABLE]
10. 4,748,234, May 31, 1988, Process for recovering refractile bodies containing heterologous proteins from microbial hosts; Glenn Dorin, et al., 530/412; 435/69.51, 69.52; 530/351, 414, 416, 417, 422, 424, 825 [IMAGE AVAILABLE]
11. 4,647,454, Mar. 3, 1987, **Stable** **interferon** .**beta**. **composition** and a method of stabilizing **interferon** .**beta**.; Samuel Cymbalista, 530/351; 424/85.4, 85.6 [IMAGE AVAILABLE]
=> d 11 ab'
'AB" IS NOT A VALID FORMAT FOR FILE 'USPAT'
ENTER DISPLAY FORMAT (CIT):ab
US PAT NO: 4,647,454 [IMAGE AVAILABLE] L3: 11 of 11
ABSTRACT:
This disclosure relates to a method of stabilizing Human Fibroblast Interferon (HFIF) known as "Interferon .beta." with polyvinyl pyrrolidone and to transportable and storable vials containing such stabilized Interferon .beta..
=> d 11 kwic
US PAT NO: 4,647,454 [IMAGE AVAILABLE] L3: 11 of 11
TITLE: **Stable** **interferon** .**beta**. **composition** and a method of stabilizing **interferon** .**beta**.
BSUM(6)
This invention relates to a novel **stable** Interferon **composition** comprised of **Interferon** .**beta**., conventional excipients, a buffer and vinyl pyrrolidone polymer, as a stabilizer.
CLMS(1)
I claim:
1. A **stable** **Interferon** .**beta**. **composition** comprising a buffered solution of highly purified **Interferon** .**beta**. and conventional excipients said solution being stabilized by 0.5 to 10% wt/volume of polyvinyl pyrrolidone.
=> s l3 and (mannitol and albumin and acetate)
19192 MANNITOL
22089 ALBUMIN
199444 ACETATE
L4 6 L3 AND (MANNITOL AND ALBUMIN AND ACETATE)
=> d 1-6
1. 5,183,746, Feb. 2, 1993, Formulation processes for pharmaceutical compositions of recombinant .beta.-; Ze'Ev Shaked, et al., 435/69.51; 424/85.6; 530/351 [IMAGE AVAILABLE]
2. 5,004,605, Apr. 2, 1991, Low pH pharmaceutical compositions of recombinant .beta.-interferon; Susan Hershenson, et al., 424/85.6; 530/351 [IMAGE AVAILABLE]
3. 4,992,271, Feb. 12, 1991, Formulation for lipophilic IL-2 proteins; Wolfgang H. Hanisch, et al., 424/85.2, 85.1, 85.4, 85.5, 85.6, 85.7; 435/811; 514/2, 8, 12, 21, 885, 970; 530/351 [IMAGE AVAILABLE]
4. 4,816,440, Mar. 28, 1989, Stable formulation of biologically active proteins for parenteral injection; James W. Thomson, 514/12; 424/85.6 [IMAGE AVAILABLE]
5. 4,748,234, May 31, 1988, Process for recovering refractile bodies containing heterologous proteins from microbial hosts; Glenn Dorin, et al., 530/412; 435/69.51, 69.52; 530/351, 414, 416, 417, 422, 424, 825 [IMAGE AVAILABLE]
6. 4,647,454, Mar. 3, 1987, **Stable** **interferon** .**beta**. **composition** and a method of stabilizing **interferon** .**beta**.; Samuel Cymbalista, 530/351; 424/85.4, 85.6 [IMAGE AVAILABLE]
=> d 1-6 kwic
US PAT NO: 5,183,746 [IMAGE AVAILABLE] L4: 1 of 6
BSUM(22)
U.S. . . . '940 patent) discloses a process for formulating interferon by mixing the interferon and a protein stabilizer, such as normal serum **albumin**, at a pH of about 10.5 to 12.5 for 5 minutes and then adjusting the pH to 7.5 to obtain. . .
BSUM(24)
Commonly . . . Proteins" outlines a high pH and a low pH process for recovering and purifying lipophilic recombinant proteins, such as human **IFN**-.**beta**. and interleukin-2, from host strains to yield a protein preparation which may be formulated into a **stable** pharmaceutical **composition**. Said **composition** carrying a therapeutically effective amount of the biologically active lipophilic protein dissolved in a non-toxic, inert, therapeutically compatible aqueous-based carrier medium at a pH of 6.8 to 7.8 also contains a stabilizer for the protein, such as human serum **albumin**, human serum **albumin** and dextrose, or human plasma protein fraction.
BSUM(25)
Commonly owned, U.S. application Ser. No. 780,551, filed Sept. 26, 1985, now U.S. Pat. No. 4,816,440, entitled "**Stable** **Formulation** of Biologically Active Proteins for Parenteral Injection," discloses pharmaceutical compositions containing **IFN**-.**beta**. or interleukin-2 dissolved in a stable carrier medium at pH 7.0 to 8.0 stabilized with sodium laurate.
BSUM(30)
There . . . processes. Further, there is a need for formulations that provide alternatives to those containing non-IFN-.beta. protein, such as those containing **albumin**.
DRAWING DESC:
DRWD(2)
FIGS. . . . graphically illustrate linear non-isothermal stability (LNS) study results comparing representative formulations of this invention with sodium laurate and human serum **albumin** (HSA) IFN-.beta. formulations. The HSA formulations are indicated in these figures as normal, high and low dose.
DETD(48)

The . . . one or more carbohydrates, and more preferably one or more sugars. Preferred stabilizing agents include, for example, sucrose, dextrose, dextran, **mannitol**, sorbitol, inositol, fructose, galactitol, xylitol, lactose, and trehalose. More preferred are dextrose and **mannitol**, and most preferred is dextrose. Additional non-carbohydrate stabilizing agents can include, for example, human serum **albumin** (HSA), which can be used alone or in combination with a carbohydrate stabilizing agent, and glycine, which is preferably used. .

DETD(52)
The . . . alone or in combination as outlined above for liquid formulations and in similar concentration ranges as well as human serum **albumin** alone or in combination with said carbohydrate stabilizers; however, such a selected carrier must not only have a stabilizing effect. . . to about 5%); the combination of dextrose (about 0.1% to about 5%, more preferably about 0.1% to about 0.2%) with **mannitol** (about 0.5% to about 5%, more preferably about 1% to about 3%; or with human serum **albumin** (HSA) at a concentration from about 1% to about 5%, more preferably about 1% to about 2%; and HSA alone. . . 2.5%). More preferred bulking/stabilizing agents are dextrose, preferably at a concentration of about 5%, and a combination of dextrose and **mannitol** at a concentration ratio by volume of from about 1/5 to about 1/20 (dextrose/**mannitol**), and more preferably at a concentration ratio of about 1/10. Such combinations of dextrose and **mannitol** are the most preferred bulking/stabilizing agents of the lyophilized formulations of this invention.

DETD(53)
For lyophilized formulations, the buffer is preferably selected from buffers, such as citrate, maleate, **acetate** and phosphate, more preferably **acetate** or phosphate, and still more Preferably phosphate, at the same preferred concentration range as indicated above for liquid formulations. Further,. . .

DETD(63)
2% **mannitol**.

DETD(76)
It . . . laurate, is employed as the primary solubilizing agent, it be in a buffer, such as phosphate, Tris HCl, or an **acetate** buffer wherein said buffer is in a molarity range of from about 5 to 40 mM, preferably 10-30 mM, and. . .

DETD(99)
The . . . preferably Tris-HCl at pH 9 to 9.8; borate at pH 9.0 to 9.8; sodium phosphate at pH 9.0 to 9.8; **acetate** at PH 9.0 to 9.8; or sodium pyrophosphate at pH 9.0 to 9.8.

DETD(114)
. . .
to 50.degree. for
10 min. under nitrogen; cool to about
25.degree. C.
Sephacryl .RTM. S200
50 mM **acetate**; pH 5.5; 1% SDS; 1
column mM EDTA
Oxidation Iodosobenzoic acid (IBA) equimolar;
protein:IBA; 0.1% SDS; 2 mM sodium
pyrophosphate; pH 9; 1 mM EDTA
Concentration pH 5.5
Sephacryl .RTM. S200
50 mM **acetate**; pH 5.5; 0.1% SDS; 1
column mM EDTA

DETD(115)

SCHEME 2B

Concentration
Sephadex .RTM. G-75
50 mM **acetate**; pH 5.5; 0.1% SDS; 1
column mM EDTA
Sephadex .RTM. G-25
0.1% sodium laurate (transfer
column component) in 10. . .

DETD(190)
The . . . Sephacryl.RTM. S200 column and collecting fractions into clean, depyrogenated vessels using an elution buffer that is composed of 50 mM **acetate**, pH 5.5, 1 mM EDTA and 1% SDS. The fractions containing
the IFN-.beta. monomer were pooled.

DETD(194)
The . . . (Sephacryl.RTM. S200-A), and fractions were collected into clean, depyrogenated vessels using an elution buffer that is composed of 50 mM **acetate**, pH 5.5, 1 mM EDTA and 0.1% SDS.

DETD(205)
Also, . . . extraction, Acid precipitation, Centrifugation, Acid precipitate solubilization, and second Reduction. The buffer is 10 mM Tris.HCl rather than 50 mM **acetate** for the gel chromatography steps on the Sephacryl.RTM. S200 columns and on the Sephadex.RTM. G-75 column. Further, such gel chromatography. . .

DETD(208)
As . . . detergents and another solubilizing agent, adjusting the pH to about physiological pH, adding an appropriate bulking/solubilizing agent, preferably dextrose or **mannitol**, pre- and sterile filtering the pool and immediately lyophilizing the formulated, neutralized product. The primary advantage of the procedures of. . .

DETD(217)
. . .
min.
A.sub.280
A.sub.280
Percent
Samples Before After Recovery

1.25% HSA (human serum
1.696 .543 32%
albumin)
0.1% SDS pH 7.5 .257 .238 93%
0.1% Laurate pH 7.5
.408 .392 96%
0.1% Durfax .RTM. 80/150 .mu.g/ml. . .

DETD(220)
The IFN-.beta. formulations listed in Table I and IFN-.beta. formulations with 0.1% sodium laurate at pH 7.5 and 1.25% normal serum **albumin** were analyzed by SDS-page electrophoresis under non-reducing conditions. Further, a sample of the purified IFN-.beta. eluate from the G-25 pool. . .

DETD(223)
The non-ionic detergent formulations listed in Table 1, as well as a 0.1% laurate formulation and a 1.25% human serum **albumin** formulation, were studied by ultracentrifugation after freeze-drying in 1.25% dextrose. Table III is a compilation of the ultracentrifugation data relating. . .

DETD(228)
. . .
Re-
Samples Treatment Before After covery

---

1 H.sub.2 O (no
None 0.400 0.367 91.8
bulking agent)
2 **Mannitol** None 0.400 0.370 92.5
3 Sorbitol None 0.409 0.378 92.4
4 Dextrose None 0.496 0.484 97.6
5 Inositol None 0.403 0.351 87.1
6 H.sub.2 O Frozen 0.388 0.384 99.0
7 **Mannitol** Frozen 0.412 0.379 92.0
8 Sorbitol Frozen 0.404 0.384 95.1
9 Dextrose Frozen 0.601 0.579 96.3
10 Inositol Frozen 0.397 0.375 94.5
11 Dextrose Frozen Slowly
0.656 0.584 89.0
12 **Mannitol** Frozen Slowly
0.296 0.249 84.1

DETD(231)
Although . . . laurate as a transfer component, as described in Example I. All the formulations tested for the LNS studies included 5% **mannitol** and were lyophilized. Final container vials were kept at 4.degree. C. until submitted for study. The linear non-isothermal stability (LNS). . .

DETD(233)
FIG. 1 shows LNS study results for normal, high and low dose human serum **albumin** formulations of **IFN**-.**beta**. as well as 1% sodium laurate formulations of **IFN**-.**beta**.. The graph of FIG. 1 indicates that the high dose HSA **formulation** is relatively more **stable** than the normal dose HSA **formulation**, which is, in turn, more **stable** than the low dose HSA and laurate formulations.
DETD(234)
FIG. 2 compares the relative stability of three **mannitol** formulations of the instant invention. The scale is the same as that for FIG. 1. From a comparison of FIGS. 1 and 2, one would predict that the Triton X305/Nopalcol **formulation** is as **stable** as the normal dose HSA formulated **IFN**-.**beta**., and that Plurafac.RTM. C-17 **formulation** is as **stable** as the high dose HSA formulated **IFN**-.**beta**..
DETD(235)
FIG. 3 illustrates the relative stability of normal and high dose HSA formulated .**beta**.-**IFN** and 0.25 mg/ml **IFN**-.**beta**. in 5% **mannitol** with 0.1% Plurafac.RTM. C-17 at pH 6.0 as well as a 0.01% Plurafac.RTM. C-17 formulation at pH 5 as represented by the diamonds on FIG. 3. The results show that the 0.1% Plurafac.RTM. C-17 **formulation** is at least as **stable** as the high-dose human serum **albumin** formulation. Further, the LNS study predicts that the 0.01% Plurafac.RTM. C-17 formulation at pH 5 will also have good long-term stability. The Trycol.RTM. LAL(12) at 0.15% formulation at pH 7 is predicted from the LNS study to be as **stable** as the high-dose HSA **formulation**, whereas the Trycol.RTM. LAL(12)-Nopalcol **formulation** should be more **stable** than the HSA normal dose **formulation**.
DETD(239)
For . . . tested per formulation. The representative formulations tested each contained one of the solubilizer/stabilizer compositions listed in Table I, supra, 5% **mannitol** and 0.25 mg/ml of IFN-.beta.. All the formulations were lyophilized and reconstituted in sterile water. Each animal was injected with. . .
DETD(245)
Mannitol Versus Dextrose Formulations
DETD(246)
Table VI shows the results of ultracentrifugation studies on **mannitol**, 2.5% **mannitol** and 5% dextrose formulations, respectively, wherein Trycol.RTM. 0.15% at pH 7 is the stabilizer/solubilizer. Ultracentrifugation data of such formulations prepared according to Example I indicate that **mannitol** in some way appears to interfere with the solubility of IFN-.beta.. Therefore, dextrose alone is considered to be a more preferred bulking/stabilizing agent than **mannitol** alone for the formulations of this invention.
DETD(247)
TABLE VI

Ultracentrifugation **Mannitol** vs. Dextrose Trycol .RTM. 0.15% pH 7.0
5% **Mannitol** 79.5%
2.5% **Mannitol** 84.5%
5% Dextrose 90.5%

DETD(249)
LNS Studies of Dextrose- and **Mannitol**-Containing Formulations
DETD(250)
LNS studies were performed on representative formulations of the instant invention to compare dextrose versus **mannitol** as the bulking/stabilizing agent therein. Trycol.RTM. LAL(12) IFN-.beta. compositions prepared as according to Example 1 were formulated with 5% dextrose and 5% **mannitol**, respectively. The LNS results are presented in FIG. 6. A comparison with a normal and high dose HSA formulated IFN-.beta.. . . be at least as stable as the normal dose HSA IFN-.beta. formulation. No difference in stability was observed between the **mannitol**- and dextrose-formulated compositions.
DETD(258)
The . . . added respectively to 10 ml aliquots of the IFN-.beta. filtrate (all percentages are weight to volume concentration ratios): 0.1% dextrose/2% **mannitol**; 0.2% dextrose/2% **mannitol**; and 0.1% dextrose/2% glycine. The pH of each 10-ml ml aliquot was then raised to about 6.0 with NaOH. The. . .
DETD(260)
. . .
and Various
Bulking/Stabilizing Agents
Bulking/Stabilizing
Ultracentrifugation
Reagents % (wt/vol.)
Recovery (%)

5% Dextrose 95%
0.1% Dextrose/2% **Mannitol** 88%
0.2% Dextrose/2% **Mannitol** 89%
0.1% Dextrose/2% Glycine 76%

DETD(262)
The UV scanning results showed very little aggregation for the formulations containing 5% dextrose, 0.1% dextrose/2% **mannitol**, and 0.2% dextrose/2% **mannitol**, as bulking/stabilizing agents; however, more aggregation was seen in the formulation containing 0.1% dextrose/2% glycine as the bulking/stabilizing agent, making. . .
US PAT NO: 5,004,605 [IMAGE AVAILABLE] L4: 2 of 6
BSUM(21)
U.S. . . . ('940 patent) discloses a process for formulating interferon by mixing the interferon and a protein stabilizer, such as normal serum **albumin**, at a pH of about 10.5 to 12.5 for 5 minutes and then adjusting the pH to 7.5 to obtain. . .
BSUM(22)
Copending, . . . Proteins" outlines a high pH and a low pH process for removing and purifying lipophilic recombinant proteins, such as human **IFN**-.**beta**. and interleukin-2, from host strains to yield a protein preparation which may be formulated into a **stable** pharmaceutical **composition**. Said **composition** carrying a therapeutically effective amount of the biologically active lipophilic protein dissolved in a not-toxic, inert, therapeutically compatible aqueous-based carrier medium at a pH of 6.8 to 7.8 also contains a stabilizer for the protein, such as human serum **albumin**, human serum **albumin** and dextrose, or human plasma protein fraction.
BSUM(23)
Copending, commonly owned, U.S. application Ser. No. 780,551, filed Sept. 26, 1985, entitled "**Stable** **Formulation** of Biologically Active Proteins for Parenteral Injection," discloses pharmaceutical compositions containing **IFN**-.**beta**. or interleukin-2 dissolved in a stable carrier medium at pH 7.0 to 8.0 stabilized with sodium laurate.
BSUM(28)
Copending, . . . U.S. Ser. No. 923,423, filed Oct. 27, 1986 and 100,679, filed Sept. 29, 1987, both entitled "Pharmaceutical Compositions of Recombinant **Beta**-**Interferon** and **Formulation** Processes" disclose and claim **stable**, pharmaceutical compositions of recombinant **interferon**-**beta** (**IFN**-.**beta**.) comprising as solubilizer/stabilizers one or more non-toxic biocompatible non-ionic polymeric detergents or a combination of one or more such non-ionic. . . solubilizing and/or stabilizing agent, such as, sodium dodecyl sulfate or glycerol. Said applications further disclose and claim methods of extracting **IFN**-.**beta**. from the disruptate of a host organism transformed to produce it and purifying the **IFN**-.**beta**. wherein the last purification step prior to formulation is a desalting step performed at a pH range or about 8.5. . . contains a fatty acid salt having from about 10 to about 12 carbons, and wherein the pH of the desalted **IFN**-.**beta**. pool is lowered to about 2 to about 4 thereby precipitating the fatty acid salt. The precipitated salt, preferably sodium. . .
BSUM(29)
There . . . art for alternative formulations of biologically active, recombinant beta-interferons, preferably that are alternatives to those containing non-IFN-.beta. protein, such as **albumin**. The present invention meets such a need.
DETD(14)
As used herein, the term "solubilizer/stabilizer" as applied to the recombinant **IFN**-.**beta**. formulations refers to essentially non-toxic and non-immunogenic compositions which alone or in combination act not only to stabilize the **IFN**-.**beta**. against denaturation and

loss of biological activity, but also to solubilize the lipophilic protein in an aqueous medium so that the pharmaceutical **formulation** constitutes a **stable** aqueous solution of **IFN**-.**beta**. protein in a pH range from about 2 to about 4, preferably from about 2.5 to about 3.5, and more. . .

DETD(31)

The compositions can further comprise an additional stabilizing agent, such as, a carbohydrate, for example, sucrose, dextrose, dextran, **mannitol**, sorbitol, inositol, fructose, galactitol, xylitol, lactose, and trehalose; or a non-carbohydrate, for example, human serum **albumin** (HSA) which can be used alone or in combination with a carbohydrate stabilizing agent. Such stabilizing agents are preferably in. . .

DETD(41)

. . .

to 50.degree. for 10
min. under nitrogen;
cool to about 25.degree. C.
Sepharcryl.RTM. S200 column
50 mM **acetate**; pH 5.5; 1% SDS;
1 mM EDTA
Oxidation Iodosobenzoic acid (IBA) equimolar;
protein; IBA; 0.1% SDS;
2 mM sokium pyrophosphate;
pH 9; 1 mM EDTA
Concentration pH 5.5
Sephacryl.RTM. 50 mM **acetate**; pH 5.5; 0.1% SDS;
1 mM EDTA
Concentration
Sephadex.RTM. G-75 column
50 mM **acetate**; pH 5.5; 0.1% SDS;
1 mM EDTA
Sephadex.RTM. G-25 column
0.1% sodium laurate (transfer
componenet) in 10. . .

DETD(95)

A . . . the precipitated sodium laurate which precipitates in step (b). The elution buffer of step (a) is preferably Tris-HCl, borate, phosphate, **acetate** or pyrophosphate, and is more preferably at pH 9.0 to 9.8.

DETD(118)

The . . . Sephacryl.RTM. S200 column and collecting fractions into clean, depyrogenated vessels using an elution buffer that is composed of 50 mM **acetate**, pH 5.5, 1 mM EDTA and 1% SDS. The fractions containing
the IFN-.beta. monomer were pooled.

DETD(122)

The . . . (Sephacryl.RTM. S200-A), and fractions were collected into clean, depyrogenated vessels using an elution buffer that is composed of 50 mM **acetate**, pH 5.5, 1 mM EDTA and 0.1% SDS.

CLMS(1)

What is claimed is:

1. A **stable** pharmaceutical **composition** of matter suitable for parenteral administration to mammals that is at a pH range of from about 2 to about 4 comprising a therapeutically effective amount of a recombinant **interferon**-.**beta**. protein dissolved in an inert carrier medium comprising as a stabilizer/solubilizer an effective amount of polyethylene glycol polymers having an. . .

CLMS(15)

15. A **stable** pharmaceutical **composition** of matter suitable for parenteral administration to mammals that is at a pH range of from about 2 to about 4 comprising a therapeutically effective amount of a recombinant **IFN**-.**beta**. protein dissolved in an inert carrier medium comprising an effective amount of a non-detergent polyhydric stabilizer/solubilizer or a combination of polyhydric non-detergent stabilizer/solubilizers selected according to a screening method comprising:

(a) purifying recombinant **IFN**-.**beta**.;
(b) lowering the pH of the **IFN**-.**beta**. to between 2 to 4;
(c) adding a non-detergent solubilizer or combination of nondetergent solubilizers; and
(d) evaluating whether the **IFN**-.**beta**. remains in solution.

CLMS(16)

16. A **stable** pharmaceutical **composition** of matter suitable for parenteral administration to mammals that is at a pH range of from about 2 to about 4 consisting of a therapeutically effective amount of a recombinant **interferon**-.**beta**. protein dissolved in an inert carrier medium comprising as a stabilizer/solubilizer an effective amount of polyethylene glycol polymers having an. . .

US PAT NO: 4,992,271 [IMAGE AVAILABLE] L4: 3 of 6

ABSTRACT:

An improved process for recovering and purifying lipophilic recombinant proteins such as human .**beta**.-**interferon** and interleukin-2 from their hosts yields a protein preparation which may be formulated into a **stable** pharmaceutical **composition** having a therapeutically effective amount of the biologically active recombinant lipophilic protein dissolved in a non-toxic, inert, therapeutically compatible aqueous-based. . . at a pH of 6.8 to 7.8 which medium also contains a stabilizer for the protein, such as human serum **albumin**, normal serum **albumin** and human plasma protein fraction.

BSUM(19)

Cancer Treatment Reports, 62, 1900-1906 (1978) and EP 89,245 disclose that native beta-interferon may be formulated directly with human serum **albumin** in a pharmaceutically compatible aqueous-based medium at a pH of 7.2-7.8.

BSUM(20)

Alpha-interferons . . . beta-interferon are not lipophilic proteins. Therefore, they can be stabilized and solubilized by adding a stabilizer such as human serum **albumin** directly to the formulation at physiological pH. In contrast, lipophilic proteins such as recombinant beta-interferon and interleukin-2 are not solubilized by addition of human serum **albumin** at pH 6.8-7.8.

BSUM(32)

Preferably, the protein in this latter formulation is .beta.-interferon or interleukin-2 and the stabilizer is human serum **albumin**, a mixture of human serum **albumin** and dextrose, human plasma protein fraction, or normal serum **albumin**.

DETD(10)

As . . . Examples of such stabilizers include, but are not limited to, proteins or carbohydrates preferably chosen from the proteins human serum **albumin** (HSA), and human plasma protein fraction (PPF), and the carbohydrates **mannitol**, sorbitol, glycerol, dextrose or a mixture thereof.

DETD(11)

The . . . for low pH formulations using IFN-.beta..sub.ser17, PPF is preferred. PPF is commercially available and is composed of at least 83% **albumin** and no more than 17% globulins (.alpha. and .beta.); no more than 1% of the proteins are gamma-globulins. The .alpha.-. . .

DETD(15)

Thus, . . . 60.degree. C. and a pH of about 8.5 to prevent aggregation of the protein. Exemplary alcohols include ethanol, butanols, glycerol, **mannitol**, sorbitol, dextrose and the like.

DETD(41)

(t) . . . stabilizing (and thereby solubilizing) the .beta.-HIFN by the addition of a 0.5-10% by weight solution of dextrose and human serum **albumin** adjusted to a pH of about 12, and maintaining a pH of 12 for 1-15 minutes;

DETD(50)

(t) adjusting the pH of a solution of human serum **albumin** or plasma protein fraction to pH 3.5;

DETD(51)

(u) adding the human serum **albumin** or plasma protein fraction to the desalted pool and incubating for 15-45 minutes;

DETD(56)

(s) adding human serum **albumin** or plasma protein fraction to the desalted pool to form a mixture;

DETD(97)

The . . . was applied to a molecular sieve column with a Sephacryl S-200.RTM.Superfine matrix. The column was equilibrated with 50 mM sodium **acetate** buffer at pH 5.5 containing 2 mM DTT and 1.0% SDS (w/v). The column was developed with the same buffer. . .

DETD(100)

The . . . and then applying the material to a fine vinyl polymer gel column. This column was equilibrated with 50 mM sodium **acetate** buffer at pH 5.5 containing 2 mM dithiothreitol and 0.1% SDS (w/v). The column was developed with the same buffer. . .

DETD(106)

Formulation With Human Serum **Albumin**/Dextrose

DETD(107)
The diafiltered interferon (.beta.-HIFN) from Example 7 was diluted to 0.25 mg/ml and incubated with pharmaceutical grade human serum **albumin** (final concentration 1.25% w/v.) for 15 minutes at pH 12. The pH of the solution was then lowered to 7.5.+-.0.3. . .
DETD(109)
In . . . Pat. No. 4,518,584 issued May 21, 1985 was purified on a G-75 Sepharose column. The G-75 pool comprised 50 mM **acetate** buffer at pH 5.5 containing 0.1% SDS and 1.88 mg/ml of the interferon. The actual concentration of SDS was 0.3-0.6. . .
DETD(130)
The solution was then applied to a Sephacryl S-200 precolumn with a buffer consisting of 1% SDS, 50 mM sodium **acetate**, 1 mM EDTA, pH 5.5.
The fractions containing highest interferon activities were pooled and concentrated by ultrafiltration with a 10. . .
DETD(133)
The . . . 0.25 M NaOH via a peristaltic pump at 5 ml/hr as needed. The IFN-.beta. solution (5 mg/ml in 50 mM **acetate** buffer, pH 5.5) was added at a flow rate of 2 ml/hr (7.0 micromole/hr) for about five hours; the o-iodosobenzoic. . .
DETD(134)
The . . . then loaded on a Sephacryl-200 column using a buffer consisting of 0.1% SDS, 1 mM EDTA, and 50 mM sodium **acetate** at pH 5.5. The monomer peak from this column was pooled and loaded on a Sephadex G-75 column using a buffer consisting of 0.1% SDS, 1 mM EDTA, and 50 mM sodium **acetate** at pH 5.5.
DETD(156)
1. Low pH Treated **Mannitol** and HSA Formulations
DETD(157)
The HPLC pool was then concentrated and diafiltered versus a buffer (Buffer K) of 50 mM **acetate**, 1 mM EDTA and 0.1% SDS. About 30 mg of the diafiltrate was concentrated and diafiltered versus 10 mM Tris.HCl. . . portions. To the respective portions was added sufficient amounts of stabilizer to yield the following final formulation concentrations: 5% (w/v) **mannitol**, 1.25% (w/v) human serum **albumin** (HSA), and 2.5% (w/v) HSA.
DETD(160)
The . . . ml H.sub.2 O was added dropwise concentrated HCl to a pH of 3. The IL-2 solution was incubated with the **albumin** solution for 15 minutes at pH 3, and then the pH was raised with 2.5 N NaOH to 7.5. The. . .
DETD(162)
B. Low pH Treated **Mannitol** Formulation
DETD(163)
A **mannitol** IL-2 formulation was prepared by mixing 49.6 ml of the G-25 desalted IL-2 pool described just above in Section A with 15 ml of 25% **mannitol** and adjusting the pH of the mixture down to 3.0 with HCl. The final concentration of **mannitol** was 2.5% (w/v). After lyophilization and reconstitution with water the sample remained clear at pH 3.0.
DETD(164)
This . . . at 2-4 and lyophilization at pH 2-4. If the pH is raised above 4, however, the carbohydrate stabilizers such as **mannitol** will not act to solubilize the lipophilic protein. Only the protein stabilizers such as HSA will solubilize the protein as. . .
CLMS(1)
What . . .
solubilized in a non-toxic, inert therapeutically compatible aqueous-based carrier medium at a pH of 6.8 to 7.8 comprising human serum **albumin**.
CLMS(6)
6. A composition according to claim 1 wherein said human serum **albumin** is present in an amount of 0.1 to 5%.
CLMS(7)
7. A composition according to claim 1 wherein said human serum **albumin** is present in a concentration range of about 0.5 to 10%.
US PAT NO: 4,816,440 [IMAGE AVAILABLE] L4: 4 of 6
BSUM(12)
U.S. Pat. No. 4,463,940 to Hanisch et al. discloses a process for formulating interferon by mixing the interferon and normal serum **albumin** at pH 12.0 for 5 minutes and then adjusting the pH to 7.5 to obtain a soluble mixture. Exposing the. . .
BSUM(13)
The only alternatives to the high pH **albumin** formulation are the addition of detergents or of chaotropic agents such as urea or guanidine hydrochloride to the formulation to. . .
BSUM(16)
Wang . . . for various drugs is provided on p. 454 and a list of stablizers, including sodium caprylate (octanoate) for normal serum **albumin**, is provided on p. 458.
BSUM(19)
The present invention provides a **stable** pharmaceutical **composition** of matter suitable for parenteral injection into animals and humans comprising a therapeutically effective amount of recombinant interleukin-2 or .**beta**.-**interferon** protein purified to contain less than 4 .mu.g sodium dodecyl sulfate per mg protein and purified from other bacterial or. . . occurs in the blood. A compound similar to sodium laurate, sodium octanoate, which is a known stabilizer for human serum **albumin**, is not an effective stabilizer for the biologically active protein IL-2.
BSUM(21)
In . . . on the exact pH of the solution, the solubilizing agent used in the process is SDS, the formulation further comprises **mannitol**, and the pH thereof is 7.5 to 7.7.
DRAWING DESC:
DRWD(27)
For . . . are inherently nontoxic and nontherapeutic. Examples of such vehicles are water, saline, Ringer's solution, dextrose solution, and 5% human serum **albumin** in water. Nonaqueous vehicles such as fixed oils and ethyl oleate may also be used. Liposomes may be used as. . . carriers. The vehicle may contain minor amounts of additives such as bulking substances or toxicity modifiers such as glycerine, lactose, **mannitol** or dextrose, oleaginous vehicles such as benzyl benzoate, lubricants, suspending agents, chelating agents, stabilizers, or substances that enhance isotonicity and. . . of about 0.1 mg/ml to 10 mg/ml, preferably 0.2 to 5 mg/ml. A preferred additive for the IL-2 formulation is **mannitol**, in a concentration of 2.5 to 5.0% by weight of the formulation.
DETD(13)
The . . . at 45K for 2 hours. The supernatant (35 ml) was loaded on a S-200 (K-50, Pharmacia) column and eluted with **acetate** pH 5.5 (50 mM), DTT (2 mM), EDTA (1 mM) and SDS (0.1%) at a rate of 1.5 ml/min. The. . .
DETD(16)
The oxidized product was separated from iodosobenzoate and iodobenzoate by G-25 column chromatography using 0.1% SDS, 50 mM sodium **acetate**, 1 mM EDTA, pH 5.5. The IL-2 was then separated from the solution by RP-HPLC as follows. The solution was. . .
DETD(19)
The IL-2 collected from the column was combined with water, sodium laurate, Na.sub.2 HPO.sub.4 and **mannitol** to a pH of 9.1 to yield final concentrations of:
DETD(20)

IL-2 0.25 mg/ml
Sodium laurate 0.07%
Na.sub.2 HPO.sub.4 10 mM
Mannitol 5%

DETD(26)

IL-2 0.25 mg/ml
Sodium laurate 0.03%
Na.sub.2 HPO.sub.4 10 mM
Mannitol 2.5%

DETD(29)
This . . . illustrates the effect of sodium laurate concentration on IL-2 solubility. The procedure of Example 2 was followed except that 5% **mannitol** was employed rather than 2.5% and no sodium laurate was added to the formulation before adjustment to pH 7.5. The. . .
DETD(30)

9.75 ml of the IL-2 pool
0.5 ml 0.5 M Na.sub.2 HPO.sub.4

5.0 ml 25% **mannitol**
11.0 ml H.sub.2 O

DETD(33)

9.75 ml of the IL-2 pool
0.5 ml 0.5 M Na.sub.2 HPO.sub.4
2.5 ml **mannitol** (25%)
0.25 ml 1% sodium laurate
10 ml H.sub.2 O

DETD(36)

9.75 ml of the IL-2 pool
0.5 ml 0.5 M Na.sub.2 HPO.sub.4
2.5 ml **mannitol** (25%)
2.5 ml 1% sodium laurate
10 ml H.sub.2 O

DETD(39)

9.75 ml of the IL-2 of this example
0.5 ml Na.sub.2 HPO.sub.4
2.5 ml 25% **mannitol**
1.5 ml 1% sodium laurate
8 ml H.sub.2 O

DETD(42)

. . .
IL-2 pool
2.5 ml 10% SDS
0.5 ml 0.5 M Na.sub.2 HPO.sub.4, pH 7
2.5 ml 25% **mannitol**
9.75 ml H.sub.2 O

DETD(46)

9.75 ml of the IL-2 pool
0.5 ml 0.5 M Na.sub.2 HPO.sub.4
2.5 ml 25% **mannitol**
0.25 ml 1% sodium octanoate
10 ml H.sub.2 O

DETD(52)
The . . . to 30 g total fatty acids in the whole blood system. The injected sodium laurate will bind quickly to serum **albumin** and enter the metabolic cycle of the bulk fatty acids, with no problem of hemolysis or sequestration of the sodium. . .
CLMS(8)
8. The composition of claim 1 further comprising **mannitol**.
CLMS(9)
9. . . . a concentration of 0.25 mg/ml, the sodium laurate is present at a concentration of 0.03-0.1% by weight per volume, and **mannitol** is present at a concentration of 2.4-5% by weight per volume.
US PAT NO: 4,748,234 [IMAGE AVAILABLE] L4: 5 of 6
DETD(57)
Optionally, . . . They are also preferably non-sensitive to water (i.e., nonhygroscopic). Specific examples of carriers that may be added include dextrose, lactose, **mannitol**, and other reduced sugars such as sorbitol, starches and starch hydrolysates derived from wheat, corn, rice, and potato, microcrystalline celluloses, and **albumin** such as human serum **albumin**. **Mannitol** and dextrose are preferred.
DETD(58)
The . . . as sterile vials, the freeze-dried residue will be clearly discernible to the naked eye. In this regard the preferred carrier, **mannitol**, yields an aesthetically acceptable (white, crystalline) residue that is not sensitive to water. The nonsensitivity of **mannitol** to water may enhance the stability of the formulation.
DETD(59)
Alternatively, . . . beta-interferons are not lipophilic proteins. Therefore, they can be stabilized and solubilized by adding a stabilizer such as human serum **albumin** at a physiological pH. In contrast, lipophilic proteins such as recombinant beta-interferon and interleukin-2 are not solubilized by addition of human serum **albumin** at pH 6.8-7.8.
DETD(60)
Copending, . . . for Lipophilic Proteins (Hanisch et al.) outlines an improved process for recovering and purifying lipophilic recombinant proteins such as human .**beta**.-**interferon** and interleukin-2 from their hosts to yield a protein preparation which may be formulated into a **stable** pharmaceutical **composition**. Such a **composition** carrying a therapeutically effective amount of the biologically active recombinant lipophilic protein dissolved in a non-toxic, inert, therapeutically compatible aqueous-based. . . carrier medium at a pH of 6.8 to 7.8 also contains a stabilizer for the protein, such as human serum **albumin**, normal serum **albumin** and human plasma protein fraction. The formulation aspects of said U.S. Ser. No. 775,751 are herein incorporated by reference as. . .
DETD(63)
The lyophilized, sterile product consists of a mixture of (1) protein, (2) carrier (dextrose or **mannitol**), (3) detergent (SDS), and (4) a small amount of buffer that will provide a physiological pH when the mixture is. . .
DETD(106)
Chromatographic . . . was loaded onto the column and fractions were collected into clean, depyrogenated vessels using an elution buffer containing 50 mM **acetate** pH 5.5, 1 mM EDTA and 0.1% SDS. Peak fractions (those falling within 70% of the maximum peak height) were. .
.
DETD(107)
Oxidized . . . hollow fiber ultrafiltration unit with a 10,000 molecular weight cutoff. The protein was then diafiltered against 0.1% SDS, 50 mM **acetate** pH 5.5 and 1 mM EDTA for three volume exchanges. In preparation for the subsequent HPLC purification, the pH of. . .
DETD(108)
Preparative . . . a depyrogenated graduated cylinder. Pooled protein was diluted by slowly adding it to a stirred buffer solution containing 50 mM **acetate** pH 5.5, 1 mM EDTA and 0.1% SDS that had 14 times the volume of the HPLC pool. Dilution was. . .
DETD(109)
The . . . was concentrated using a hollow-fiber ultrafiltration unit with a 10,000 molecular weight cutoff. The concentrate was diafiltered against 50 mM **acetate** pH 5.5, 1 mM EDTA and 0.1% SDS with three volume exchanges.
DETD(110)
The . . . IL-2 monomer fractions from higher molecular weight oligomers of the protein. The column was eluted with buffer containing 50 mM **acetate** pH 5.5, 1 mM EDTA and 0.1% SDS, and IL-2 monomer fractions
were pooled. Immediately preceding formulation, the protein was. . .
DETD(111)
Purified IL-2 was formulated in 10 mM sodium phosphate pH 7.5 with 5% **mannitol** (w/v). It was prefiltered through a 0.45 .mu.m filter and sterile filtered through a 0.22 .mu.m filter. Finally, the product. . .
DETD(152)
The . . . Sephacryl.RTM. S200 column and collecting fractions into clean, depyrogenated vessels using an elution buffer that is composed of 50 mM **acetate**, pH 5.5, 1 mM EDTA and 1% SDS. The fractions containing
the IFN-.beta. monomer were pooled.
DETD(156)
The . . . (Sephacryl.RTM. S200-A), and fractions were collected into clean, depyrogenated vessels using an elution buffer that is composed of 50 mM **acetate**, pH 5.5, 1 mM EDTA and 0.1% SDS.
DETD(161)
The purified IFN-.beta. was formulated with Normal Serum **Albumin** (Human) USP (NSA) and 50% Dextose Monohydrate. Normal Serum **Albumin**
was diluted with water for injection to give a final concentration of 1.25% for 0.05 and 0.25 mg/ml IFN-.beta. formulations. . .
US PAT NO: 4,647,454 [IMAGE AVAILABLE] L4: 6 of 6
TITLE: **Stable** **interferon** .**beta**. **composition** and a method of stabilizing **interferon** .**beta**.
BSUM(6)
This invention relates to a novel **stable** Interferon **composition** comprised of **Interferon** .**beta**., conventional excipients, a buffer and vinyl pyrrolidone polymer, as a stabilizer.
BSUM(7)
This . . . of stabilising Interferon .beta., wherein a highly

purified Interferon .beta. solution admixed with known excipients therefor is dialysed against an **acetate** buffer solution--pH=3.5, for about 48 hours, the resulting Interferon solution is subjected to sterile filtration, the filtrate is admixed with. . .
BSUM(8)
The preferred excipients are **mannitol** and human serum **albumin** (HSA). The **acetate** buffer used contains sodium **acetate** and sufficient acetic acid to adjust the pH to 3.5 P.V.P. marketed as POVIDONE, having a molecular weight of about. . .
DETD(3)
20 lts of aqueous **acetate** buffer solution having a pH=3.5 are prepared by dissolving 21.6 cc of acetic acid and 4.02 gms of sodium **acetate** in the required volume of distilled water.
DETD(4)
The inner surface of a sterile dialysis bag is wetted with sufficient concentrated human serum **albumin** to result in a 1% concentration in a highly purified Interferon .beta. solution, having a specific activity of about 10.sup.7. . .
DETD(5)
The resulting solution is dialysed against the **acetate** buffer of pH 3.5 and at a temperature of 4.degree. C. for about 48 hours at a ratio of 1:100. . .
DETD(6)
The dialysed Interferon .beta. preparation is admixed with **mannitol** 0.5% wt/volume final concentration and with P.V.P. at a 2% final concentration approximately prior to or following filtration through a sterile filter, previously impregnated with sufficient concentrated human serum **albumin** to raise the **albumin** concentration in the filtrate to 2% wt/volume. The filtrate is collected in a sterile bottle.
DETD(7)
The P.V.P. concentration is then finally adjusted to 2% wt/volume and the concentration of **mannitol** to 0.5% wt/volume, if necessary. The final volume of the solution is adjusted with sterile **acetate** buffer.
DETD(10)

Sodium **Acetate** AG
0.4 mgm
Sodium Chloride AG
1.8 mgm
Human Serum **Albumin**
40.0 mgm
Fraction V
Mannitol AG 10.0 mgm
PVP - Stabilizer 40.0 mgm
Human Fibroblast Interferon
1.0 10.sup.6 I.U. (approximately)

DETD(11)
The . . . comparative data are reported in these tables for Interferon .beta. compositions without P.V.P. and compositions containing sucrose or Human Serum **Albumin** in various concentrations instead of P.V.P.; Tables (4), (5) and (6) illustrate the relationship between the titer of inventive Interferon. . .
DETD(12)
Comparative data for Interferon .beta. compositions admixed with Sucrose or Human Serum **albumin** are again given.
CLMS(1)
I claim:
1. A **stable** **Interferon** .**beta**. **composition** comprising a buffered solution of highly purified **Interferon** .**beta**. and conventional excipients said solution being stabilized by 0.5 to 10% wt/volume of polyvinyl pyrrolidone.
CLMS(2)
2. A composition as claimed in claim 1, wherein the excipients are **mannitol** and human serum **albumin**.
CLMS(3)
3. A composition as claimed in claims 1 or 2, wherein the buffer is an **acetate** buffer having a pH of 3.5.
CLMS(8)
8. . . . of stabilizing Interferon .beta., wherein a highly purified Interferon .beta. solution, admixed with known excipients therefor is dialysed against an **acetate** buffer solution, the resulting Interferon solution is admixed with 0.5 to 10% wt/volume of polyvinyl pyrrolidone prior to or following. . .

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COPYRIGHT (C) 1997 Japan Science and Technology Corporation (JST)
=> s (ifn or interferon) (w) beta
L1 2514 FILE MEDLINE
L2 3034 FILE BIOSIS
L3 2344 FILE CA
L4 151 FILE WPIDS
L5 494 FILE JICST-EPLUS TOTAL FOR ALL FILES
L6 8537 (IFN OR INTERFERON) (W) BETA
=> s (low pH) or (pH (3a) (3.0 or 4.0 or 3.1 or 3.2 or 3.5 or 3.6 or 3.7 or 3.8 or 3.9))
L7 9349 FILE MEDLINE
L8 17851 FILE BIOSIS
L9 53471 FILE CA
<------User Break------> SEARCH ENDED BY USER
SEARCH ENDED BY USER <------User Break------> SEARCH ENDED BY USER
SEARCH ENDED BY USER
=> del l7-9
DELETE L7-L9? (Y)/N:y
'L7-L9' DELETED
=> s (low pH) or (pH (3a) (3.0 or 4.0))
L7 6911 FILE MEDLINE
L8 12731 FILE BIOSIS
L9 29241 FILE CA
L10 4914 FILE WPIDS
L11 927 FILE JICST-EPLUS TOTAL FOR ALL FILES
L12 54724 (LOW PH) OR (PH (3A) (3.0 OR 4.0))
=> s l6 and l12
L13 1 FILE MEDLINE
L14 3 FILE BIOSIS
L15 8 FILE CA
L16 3 FILE WPIDS
L17 0 FILE JICST-EPLUS TOTAL FOR ALL FILES
L18 15 L6 AND L12
=> dup rem l18
PROCESSING COMPLETED FOR L18
L19 11 DUP REM L18 (4 DUPLICATES REMOVED)
=> d 1-11 bib ab
L19 ANSWER 1 OF 11 BIOSIS COPYRIGHT 1997 BIOSIS
AN 96:331010 BIOSIS
DN 99053366
TI Production of interferon-gamma by chicken T cells.
AU Lowenthal J W; Digby M R; York J J
CS CSIRO Div. Animal Health, Animal Health Res. Lab., Private Bag No. 1, Parkville, Victoria 3052, Australia
SO Journal of Interferon and Cytokine Research 15 (11). 1995. 933-938.
ISSN: 1079-9907
LA English
AB In mammals, interferon (IFN)-alpha/beta (type I) is typically resistant to exposure to heat and *low* *pH* , whereas IFN-gamma (type II) is labile. Type I IFN has been described in birds; however, the existence of type II IFN has been questioned. We have generated cloned chicken T cell lines that produce high levels of IFN and have studied the physiochemical properties of this IFN activity to determine whether it represents the type I or type II IFN found in mammals. When incubated at 60 degree C, the IFN activity present in the supernatants from these chicken T cells was found to be labile, two-thirds of the activity being lost within 1-2 minutes. Consistent with IFN-gamma activity, this heat-labile IFN was also sensitive to exposure to pH 2. The heat-resistant IFN lost activity at a much slower rate (half-life gt 2 h at 60 degree C) and was also resistant to exposure to pH 2, which is characteristic of IFN-alpha/beta. To confirm further the presence of IFN-gamma activity, these T cell supernatants were assayed for their ability to activate macrophages as measured by induction of nitrite production. Consistent with mammalian IFN-gamma, the nitrite-inducing activity was found to be heat labile, with over 90% of the activity lost within 5 minutes of heating. These results show that chicken T cells produce IFN-gamma.
L19 ANSWER 2 OF 11 MEDLINE DUPLICATE 1
AN 90257413 MEDLINE
TI Conformation and activity of recombinant human fibroblast *interferon* - *beta* .
AU Boublik M; Moschera J A; Wei C; Kung H F
CS Roche Institute of Molecular Biology, Roche Research Center, Nutley, NJ 07110..
NC NO1-CO-74102 (NCI)
SO JOURNAL OF INTERFERON RESEARCH, (1990 Apr) 10 (2) 213-9.
Journal code: IJI. ISSN: 0197-8357.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 9008
AB Conformation of highly purified recombinant human fibroblast *interferon* - *beta* (rHuIFN-beta) was correlated with its biological activity. The extent of ordered secondary structure was determined by circular dichroic (CD) spectroscopy in various buffer conditions to establish conditions of protein stability and its potential for helix formation. The highest "helicity" (about 50 +/- 5% of alpha-helices) and the highest antiviral activities (4-10 x 10(7) units/mg) were found in 50% ethylene glycol, 1 M NaCl and 0.05 M Na3PO4, pH 7.2 (Buffer I); 80 mM citric acid, 20 mM Na2HPO4, pH 2.9 (Buffer II); and 25 mM NH4OAc, 125 mM NaCl, pH 5.1 (Buffer III). Both helicity and antiviral activity of the *IFN* - *beta* decrease in parallel with denaturation by urea, heat, and/or by repeated cycles of freezing and thawing. *Low* *pH* (pH 2.9 Buffer II) exhibits a distinct stabilizing effect on the structure and antiviral activity of *IFN* - *beta* against heat denaturation.
L19 ANSWER 3 OF 11 CA COPYRIGHT 1997 ACS DUPLICATE 2
AN 112:84197 CA
TI *Low* *pH* pharmaceutical compositions of recombinant beta-interferon
IN Hershenson, Susan I.; Thomson, Jody
PA Cetus Corp., USA
SO PCT Int. Appl., 35 pp.
CODEN: PIXXD2
PI WO 8905158 A1 890615
DS W: AU, DK, FI, JP, NO
RW: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE
AI WO 88-US4307 881202
PRAI US 87-131375 871210
DT Patent
LA English
AB A stable parenteral compn. having pH of 2-4 comprises a recombinant *interferon* -. *beta* . (*IFN* -. *beta* .) dissolved in an inert carrier contg. glycerol or polyethylene glycol (mol. wt. 190-1600) as a stabilizer/solubilizer. The strain of *IFN* -. *beta* .ser17-producing Escherichia coli carrying plasmid -pSY2501 was cultured; the cells were disrupted and extd. with 2-butanol; the ext. was purified by centrifugation, precolumn chromatog., ultrafiltration, and column chromatog.; the final supernatant was then stabilized by adding either 25% glycerol or 25% PEG-300. The formulations remained sol. after 1 wk storage at 4.degree.. Cytopathic effect assay results showed the formulations maintained bioactivity at 4.degree. during 1 wk.
L19 ANSWER 4 OF 11 CA COPYRIGHT 1997 ACS
AN 110:179532 CA
TI Pharmaceutical injections containing recombinant beta-interferons and nonionic surfactants and sugars as stabilizers
IN Shaked, Zeev; Stewart, Tracy; Thomson, Jody; Thomson, James William; Taforo, Terrance; Hershenson, Susan
PA Cetus Corp., USA
SO Eur. Pat. Appl., 83 pp.
CODEN: EPXXDW
PI EP 270799 A1 880615
DS R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE
AI EP 87-115693 871026

PRAI US 86-923423 861027
DT Patent
LA English
AB A stable pharmaceutical compn. for parenteral administration comprises a recombinant *interferon* -. *beta* . (*IFN* -. *beta* .) protein dissolved in an inert carrier medium contg. .gtoreq.1 biocompatible nonionic polymeric detergent(s) as a solubilizer or stabilizer. The strain of *IFN* -. *beta* .ser17-producing E. coli carrying plasmid pSY2501 was cultured. The refractile bodies contg. *IFN* -. *beta* .ser17 protein were harvested, concd., and disrupted; EDTA was added to kill residual bacterial and sucrose was added to create a concn. gradient of 1.1-1.25 g/mL and the soln. was centrifuged. The pellet was solubilized in phosphate-buffered saline with 2% Na dodecyl sulfate and dithiothreitol and extd. with 2-butanol. The ext. was again mixed with 0.1% Na dodecyl sulfate in phosphate-buffered saline and dithiothreitol; the mixt. was centrifuged and the pellet contained 81% *IFN* -. *beta* .. The pellet was then processed by Sephacryl S200 pre-column chromatog., oxidized by o-iodobenzoic acid, concd., and purified by Sephadex G-75 column. The desalting step was performed at pH 9.2 with Sephadex G-25 column equilibrated with 0.1% Na laurate and the pH of the eluate was lowered to *pH* *3* . *0* to ppt. the Na laurate. The mixt. was centrifuged and the supernatant was stabilized by adding 0.15% Trycol LAL-12; the pH was raised to .apprx.7.0 with NaOH and 5g dextrose was then added; finally the soln. was sterile-filtered and the dosage amts. of *IFN* -. *beta* .ser17 (0.25 mg) were filled into vials and frozen to between -35 and -45.degree.. A preferred lyophilized normal dose formulation comprises recombinant *IFN* -. *beta* . 0.25 mg/mL, polyoxyethylene lauryl ether 0.15% by vol., Na phosphate buffer 20 mM, dextrose 0.2%, and mannitol 2%. These *IFN* -. *beta* . formulations are at least as stable as human serum albumin-contg. formulations and they do not require strong solubilizing agents such as SDS.

L19 ANSWER 5 OF 11 CA COPYRIGHT 1997 ACS
AN 108:210189 CA
TI Manufacture of liposomes containing interferons
IN Yagi, Kunio; Kojima, Nakao
PA Vitamin Kenkyusho K. K., Japan
SO Jpn. Kokai Tokkyo Koho, 6 pp.
CODEN: JKXXAF
PI JP 62283934 A2 871209 Showa
AI JP 86-125631 860602
DT Patent
LA Japanese
AB An interferon is enclosed by a membrane consisting of phosphatidylcholines, cholesterol, and sulfatides. Lipids (60 .mu.mol) contg. egg yolk phosphatidylcholine, cholesterol, and sulfatides (5:4:1 mol ratio) were dissolved in CHCl3 in a round-bottom flask, and then the solvent was evapd., forming a thin film at the bottom. To the container were added 2 mL 20 mM NaCl Purificn. comprises (i) contacting a human *IFN* - *beta* soln. with an anti-human *IFN* - *beta* -antibody insolubilised carrier, (ii) dissolving the substance adsorbed on the carrier with an eluent (A), (iii) contacting the dissolved eluate with a high speed liq. chromatography carrier to which a hydrophobic gp. is bonded and (iv) dissolving the human *IFN* - *beta* adsorbed on the chromatography-carrier with an eluent (B).
Suitable carriers in (i) are cellulose, agarose, crosslinked dextran, polyacrylamide or porous glass. Pref. eluent (A) is an acidic buffer having an ionic strength of 0.05 or less and *pH* of 1.5- *3* . *0* , such as 0.1M-citric acid or 0.1-0.2M-glycine hydrochloride, which may opt. contain a water-soluble organic solvent (e.g. glycerol, ethylene-glycol) or a surfactant. Elution (B) is pref. a combination of water-soluble organic solvent and buffer. The buffers are, e.g. trifluoro-acetic acid, formic acid/pyridine, phosphate, acetate or perchlorate buffers. Organic solvents are, e.g. acetonitrile, 2-propanol, 1-propanol, ethanol or methanol.
USE/ADVANTAGE - Human *IFN* - *beta* of high purity may be isolated with high yield. The process is esp. useful in purificn. of human IFN-B as produced by genetic recombination.

0/0
L19 ANSWER 8 OF 11 CA COPYRIGHT 1997 ACS
AN 102:129976 CA
TI Monoclonal antibodies for purification and RIA of natural and recombinant human interferon-.alpha., -.beta. and -.gamma.
AU Novick, D.; Eshhar, Z.; Fischer, D. G.; Mory, Y.; Chernajovsky, Y.; Revel, M.; Rubinstein, M.
CS Dep. Virol., Weizmann Inst. Sci., Rehovot, 76100, Israel
SO Protides Biol. Fluids (1985), Volume Date 1984, 32, 945-8
CODEN: PBFPA6; ISSN: 0079-7065
DT Journal
LA English
AB Monoclonal antibodies were prepd. against 3 major groups of human interferons (IFNs). A novel screening procedure was developed and used for the selection of specific hybridomas. Immunoadsorbents prepd. from these antibodies were used for purifn. to homogeneity of human IFNs from various sources. *Low* *pH* was used for recovery of IFN-.alpha. and -.beta., high pH was used for IFN-.gamma.. Both recombinant IFN-.alpha. from Escherichia coli and several types of cellular IFN-.alpha. were purified to homogeneity as detd. by SDS-polyacrylamide gel electrophoresis and by the specific activity. *IFN* -. *beta* . produced by either normal fibroblasts or by recombinant CHO cells was purified to homogeneity by immunoaffinity chromatog. Similarly, IFN-.gamma. produced by either peripheral blood mononuclear cells or by recombinant CHO cells was purified to homogeneity in 1 step. Double antibody solid phase RIAs for IFN-.alpha., -.beta. and -.gamma. were developed.

L19 ANSWER 9 OF 11 BIOSIS COPYRIGHT 1997 BIOSIS
AN 84:321316 BIOSIS
DN BA78:57796
TI INTERFERON RECEPTOR INTERACTION INTERNALIZATION OF INTERFERON ALPHA-2
AND MODULATION OF ITS RECEPTOR ON HUMAN CELLS.
AU SARKAR F H; GUPTA S L
CS SLOAN-KETTERING INST. CANCER RES., 410 EAST-68TH ST., NEW YORK CITY,
N.Y., USA 10021.
SO EUR J BIOCHEM 140 (3). 1984. 461-468. CODEN: EJBCAI ISSN: 0014-2956
LA English
AB Human interferon-.alpha.2 (HuIFN-.alpha.2) binds to a specific macromolecular receptor on human cells as identified by cross-linking with bifunctional cross-linking reagents and analysis by polyacrylamide gel electrophoresis. Experiments to investigate the fate of the interferon-receptor complex on the cell surface under conditions which lead to cellular response are reported. As analyzed by cross-linking and gel electrophoresis, the interferon-receptor complex, formed on incubation with 125I-IFN-.alpha.2 at 4.degree. C, persisted at the cell [Daudi human lymphoblastoid line] surface for several hours at 4.degree. C; if the cells were switched to 37.degree. C, there was a rapid decline in the complex, apparently due to a loss of the interferon receptors from the cell surface. This was associated with an internalization of the 125I-interferon as indicated by the fact that, on incubation at 37.degree. C, an appreciable fraction of the cell-associated interferon (.apprxeq. 50%) became resistant to trypsin digestion, or dissociation on incubation in growth medium or *low* - *pH* buffer. A large fraction of the trypsin-resistant (internalized) 125I-labeled material migrated as intact interferon in polyacrylamide gels, and it was immunoprecipitated by anti-(HuIFN-.alpha.)antibodies but not by anti-(HuIFN-.beta.)antibodies. The bulk of the internalized 125I-interferon was recovered in a particulate fraction and, on cross-linking with disuccinimidyl suberate, a 150,000 MW complex could be detected. Thus, interferon may be internalized as a complex with the receptor, which may account for the loss of the interferon-receptors on the cell surface. This modulation of the IFN-.alpha./.beta. receptors was induced by HuIFN-.alpha. and HuIFN-.beta., but not by HuIFN-.gamma.. The recovery of the IFN-.alpha./.beta. receptors, lost upon incubation with HuIFN-.alpha., took several hours and required protein syntehsis. The significance of the results is discussed.

L19 ANSWER 10 OF 11 CA COPYRIGHT 1997 ACS
AN 98:33060 CA

TI Preparation of .beta.-type interferon
PA Wakunaga Pharmaceutical Co., Ltd., Japan
SO Jpn. Kokai Tokkyo Koho, 10 pp.
CODEN: JKXXAF
PI JP 57175125 A2 821028 Showa
AI JP 81-59516 810420
DT Patent
LA Japanese
AB .beta.-Type interferons are produced from a culture of human thymus lymphoblasts. For example, a lymphoblast RPMI 8402 strain was cultured and treated with Sendai virus. The cell d. in the medium was 5 .times. 106. After 24 h culture at 37.degree., the medium was centrifuged at 3000 rpm for 10 min, and the supernatant collected and irradiated with UV light for 2 h to inactivate the virus. The soln. was cooled, treated with (NH4)2SO4, and centrifuged at 9000 rpm for 30 min. The sediment was dissolved in PBS(-) and dialyzed against PBS(-) for 3 days. The *pH* was adjusted to *4* . *0* , and the soln. subjected to SP-Sephadex C-25 chromatog., and eluted with 0.1M Na borate at pH 8.0 to obtain .beta.-interferon.
L19 ANSWER 11 OF 11 CA COPYRIGHT 1997 ACS
AN 96:83901 CA
TI A monoclonal antibody to murine *interferon* - *beta*
AU Trapman, J.; Bosveld, I. J.; Vonk, W. P.; Hekman, R. A. C. P.; De Jonge, P.; Van Ewijk, W.
CS Dep. Pathol., Erasmus Univ., Rotterdam, 3000 DR, Neth.
SO Biol. Interferon Syst., Proc. Int. Meet. (1981), 77-80. Editor(s): De Maeyer, Edward; Galasso, George; Schellekens, Huub. Publisher: Elsevier North-Holland Biomed. Press, Amsterdam, Neth.
CODEN: 47EBAO
DT Conference
LA English
AB Monoclonal antibodies (IgG) to mouse *interferon* -. *beta* . were obtained from hybridomas. The IgG were coupled to CNBr-activated Sepharose. Columns prepd. from this adsorbent retained *interferon* -. *beta* ., which could then be eluted with a *low* *pH* buffer. Recovery of activity was 80-100%. The material migrated as a single band on SDS-gel electrophoresis and has a mol. wt. of 32,000-34,000. This is a simple 1-step procedure for interferon purifn. and can be used for rapid purifn. of large quantities of material.
=> s (ifn or interferon) and l12
L20 45 FILE MEDLINE
L21 48 FILE BIOSIS
L22 68 FILE CA
L23 22 FILE WPIDS
L24 0 FILE JICST-EPLUS TOTAL FOR ALL FILES
L25 183 (IFN OR INTERFERON) AND L12
=> s l25 and mannitol and albumin
L26 0 FILE MEDLINE
L27 0 FILE BIOSIS
L28 1 FILE CA
L29 0 FILE WPIDS
L30 0 FILE JICST-EPLUS TOTAL FOR ALL FILES
L31 1 L25 AND MANNITOL AND ALBUMIN
=> d ab bib
L31 ANSWER 1 OF 1 CA COPYRIGHT 1997 ACS
AB A stable pharmaceutical compn. for parenteral administration comprises a recombinant *interferon* -.beta. (*IFN* -.beta.) protein dissolved in an inert carrier medium contg. .gtoreq.1 biocompatible nonionic polymeric detergent(s) as a solubilizer or stabilizer. The strain of *IFN* -.beta.ser17-producing E. coli carrying plasmid pSY2501 was cultured. The refractile bodies contg. *IFN* -.beta.ser17 protein were harvested, concd., and disrupted; EDTA was added to kill residual bacterial and sucrose was added to create a concn. gradient of 1.1-1.25 g/mL and the soln. was centrifuged. The pellet was solubilized in phosphate-buffered saline with 2% Na dodecyl sulfate and dithiothreitol and extd. with 2-butanol. The ext. was again mixed with 0.1% Na dodecyl sulfate in phosphate-buffered saline and dithiothreitol; the mixt. was centrifuged and the pellet contained 81% *IFN* -.beta.. The pellet was then processed by Sephacryl S200 pre-column chromatog., oxidized by o-iodobenzoic acid, concd., and purified by Sephadex G-75 column. The desalting step was performed at pH 9.2 with Sephadex G-25 column equilibrated with 0.1% Na laurate and the pH of the eluate was lowered to *pH* *3* . *0* to ppt. the Na laurate. The mixt. was centrifuged and the supernatant was stabilized by adding 0.15% Trycol LAL-12; the pH was raised to .apprx.7.0 with NaOH and 5g dextrose was then added; finally the soln. was sterile-filtered and the dosage amts. of *IFN* -.beta.ser17 (0.25 mg) were filled into vials and frozen to between -35 and -45.degree.. A preferred lyophilized normal dose formulation comprises recombinant *IFN* -.beta. 0.25 mg/mL, polyoxyethylene lauryl ether 0.15% by vol., Na phosphate buffer 20 mM, dextrose 0.2%, and *mannitol* 2%. These *IFN* -.beta. formulations are at least as stable as human serum *albumin* -contg. formulations and they do not require strong solubilizing agents such as SDS.
AN 110:179532 CA
TI Pharmaceutical injections containing recombinant beta-interferons and nonionic surfactants and sugars as stabilizers
IN Shaked, Zeev; Stewart, Tracy; Thomson, Jody; Thomson, James William; Taforo, Terrance; Hershenson, Susan
PA Cetus Corp., USA
SO Eur. Pat. Appl., 83 pp.
CODEN: EPXXDW
PI EP 270799 A1 880615
DS R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE
AI EP 87-115693 871026
PRAI US 86-923423 861027
DT Patent
LA English
=> s l25 and (mannitol or albumin)
L32 0 FILE MEDLINE
L33 1 FILE BIOSIS
L34 6 FILE CA
L35 2 FILE WPIDS
L36 0 FILE JICST-EPLUS TOTAL FOR ALL FILES
L37 9 L25 AND (MANNITOL OR ALBUMIN)
=> s l37 not l9
L38 0 FILE MEDLINE
L39 0 FILE BIOSIS
L40 0 FILE CA
L41 0 FILE WPIDS
L42 0 FILE JICST-EPLUS TOTAL FOR ALL FILES
L43 0 L37 NOT L9
=> d his (FILE 'HOME' ENTERED AT 16:02:23 ON 03 MAY 1997)
FILE 'MEDLINE, BIOSIS, CA, WPIDS, JICST-EPLUS' ENTERED AT 16:02:55
ON 03 MAY 1997
L1 2514 FILE MEDLINE
L2 3034 FILE BIOSIS
L3 2344 FILE CA
L4 151 FILE WPIDS
L5 494 FILE JICST-EPLUS
TOTAL FOR ALL FILES
L6 8537 S (IFN OR INTERFERON) (W) BETA
L7 6911 FILE MEDLINE
L8 12731 FILE BIOSIS
L9 29241 FILE CA
L10 4914 FILE WPIDS
L11 927 FILE JICST-EPLUS
TOTAL FOR ALL FILES
L12 54724 S (LOW PH) OR (PH (3A) (3.0 OR 4.0))
L13 1 FILE MEDLINE
L14 3 FILE BIOSIS
L15 8 FILE CA
L16 3 FILE WPIDS
L17 0 FILE JICST-EPLUS
TOTAL FOR ALL FILES
L18 15 S L6 AND L12
L19 11 DUP REM L18 (4 DUPLICATES REMOVED)
L20 45 FILE MEDLINE
L21 48 FILE BIOSIS
L22 68 FILE CA
L23 22 FILE WPIDS
L24 0 FILE JICST-EPLUS
TOTAL FOR ALL FILES

L25 183 S (IFN OR INTERFERON) AND L12
L26 0 FILE MEDLINE
L27 0 FILE BIOSIS
L28 1 FILE CA
L29 0 FILE WPIDS
L30 0 FILE JICST-EPLUS
TOTAL FOR ALL FILES
L31 1 S L25 AND MANNITOL AND ALBUMIN
L32 0 FILE MEDLINE
L33 1 FILE BIOSIS
L34 6 FILE CA
L35 2 FILE WPIDS
L36 0 FILE JICST-EPLUS
TOTAL FOR ALL FILES
L37 9 S L25 AND (MANNITOL OR ALBUMIN)
L38 0 FILE MEDLINE
L39 0 FILE BIOSIS
L40 0 FILE CA
L41 0 FILE WPIDS
L42 0 FILE JICST-EPLUS
TOTAL FOR ALL FILES
L43 0 S L37 NOT L9
=> dup rem l25
PROCESSING COMPLETED FOR L25
L44 110 DUP REM L25 (73 DUPLICATES REMOVED)
=> d 1-10 ti
L44 ANSWER 1 OF 110 WPIDS COPYRIGHT 1997 DERWENT INFORMATION LTD
TI Enrichment of protein allowing eluted protein to be stored without further treatment - uses copper chelate-activity chromatography, elution is carried out in one step.
L44 ANSWER 2 OF 110 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 1
TI Replacing succinate with glycolate buffer improves the stability of lyophilized *interferon* -gamma.
L44 ANSWER 3 OF 110 CA COPYRIGHT 1997 ACS
TI Stable pharmaceutical compositions containing hybrid .alpha.-*Interferon*
L44 ANSWER 4 OF 110 WPIDS COPYRIGHT 1997 DERWENT INFORMATION LTD
TI A stable soln. of hybrid-alpha- *interferon* - used in the treatment of diseases e.g. Hairy-cell leukaemia.
L44 ANSWER 5 OF 110 MEDLINE DUPLICATE 2
TI Stability of recombinant consensus *interferon* to air-jet and ultrasonic nebulization.
L44 ANSWER 6 OF 110 MEDLINE DUPLICATE 3
TI Production of *interferon* -gamma by chicken T cells.
L44 ANSWER 7 OF 110 CA COPYRIGHT 1997 ACS
TI Cytokines modulate the expression of specific proteins of the contractile apparatus in rat myocytes
L44 ANSWER 8 OF 110 BIOSIS COPYRIGHT 1997 BIOSIS
TI Changes in LAK susceptibility of tumor cells as their MHC class I antigen expression levels regenerate after treatment at *pH* *3* . *0* .
L44 ANSWER 9 OF 110 WPIDS COPYRIGHT 1997 DERWENT INFORMATION LTD
TI Stabilised aq. compsns. of gamma- *interferon* provide 2-30 doses - for repeated admin. in the treatment of e.g. renal cell carcinoma..
L44 ANSWER 10 OF 110 MEDLINE DUPLICATE 4
TI Affinity purification and characterization of (2'-5')oligo(adenylate)-dependent RNase from mouse spleen.
=> s l25 and stabl?
L45 10 FILE MEDLINE
L46 8 FILE BIOSIS
L47 11 FILE CA
L48 6 FILE WPIDS
L49 0 FILE JICST-EPLUS TOTAL FOR ALL FILES
L50 35 L25 AND STABL?
=> dup rem l50
PROCESSING COMPLETED FOR L50
L51 20 DUP REM L50 (15 DUPLICATES REMOVED)
=> d 1-20 bib ab
L51 ANSWER 1 OF 20 CA COPYRIGHT 1997 ACS
AN 123:93267 CA
TI *Stable* pharmaceutical compositions containing hybrid .alpha.-*Interferon*
IN Lowther, Nicholas; Allen, John D.; Howes, Colin
PA Ciba-Geigy A.-G., Switz.
SO Can. Pat. Appl., 14 pp.
CODEN: CPXXEB
PI CA 2129921 AA 950214
AI CA 94-2129921 940811
PRAI GB 93-16849 930813
GB 94-5879 940324
DT Patent
LA English
AB A *stable* aq. soln. of hybrid .alpha.- *Interferon* (I) contains as the stabilizer a buffer at a *pH* of *3* . *0* -5.0. The amt. of I, after storage for 136 days at 4.degree. in a soln. (0.3mg/mL) contg. citrate buffer (*pH* = *4* . *0*), was 94.00%.
L51 ANSWER 2 OF 20 WPIDS COPYRIGHT 1997 DERWENT INFORMATION LTD
AN 95-099985 [14] WPIDS
DNC C95-045402
TI A *stable* soln. of hybrid-alpha- *interferon* - used in the treatment of diseases e.g. Hairy-cell leukaemia.
DC B04
IN ALLEN, J D; HOWES, C; LOWTHER, N; HOWENS, C
PA (CIBA) CIBA GEIGY AG; (CIBA) CIBA GEIGY CORP
CYC 10
PI EP 641567 A1 950308 (9514)* EN 9 pp
AU 9468939 A 950223 (9515)
NO 9402983 A 950214 (9515)
FI 9403705 A 950214 (9518)
ZA 9406073 A 950329 (9519) 15 pp
CA 2129921 A 950214 (9520)
JP 07145070 A 950606 (9531) 6 pp
TW 249202 A 950611 (9533)
NZ 264218 A 950726 (9535)
HU 68692 T 950728 (9536)
US 5609868 A 970311 (9716) 6 pp
ADT EP 641567 A1 EP 94-305930 940810; AU 9468939 A AU 94-68939 940805;
NO 9402983 A NO 94-2983 940812; FI 9403705 A FI 94-3705 940810; ZA 9406073 A ZA 94-6073 940812; CA 2129921 A CA 94-2129921 940811; JP 07145070 A JP 94-184654 940805; TW 249202 A TW 94-106518 940718; NZ 264218 A NZ 94-264218 940811; HU 68692 T HU 94-2356 940812; US 5609868 A US 94-288671 940810
PRAI GB 93-16849 930813; GB 94-5879 940324
AB EP 641567 A UPAB: 950412
A *stable* soln. of hybrid alpha- *interferon* which contains, as the stabiliser, a buffer at pH 3-5 is claimed.
USE - The soln. is used in the treatment of disease e.g. Hairy-cell leukaemia, Karposi's sarcoma in AIDS, chronic Non-A, Non-B hepatitis and basal cell carcinoma. The soln. is administered by injection at concns. of 0.1-1.5 (pref. 0.2-0.4) mg/ml.
ADVANTAGE - The hybrid alpha- *interferon* maintains its disaggregated state which eliminates any possible adverse immunogenic effects and/or inconsistent dosing during therapy.
Dwg.0/0
L51 ANSWER 3 OF 20 WPIDS COPYRIGHT 1997 DERWENT INFORMATION LTD
AN 95-006357 [01] WPIDS
DNN N95-005231 DNC C95-002155
TI Stabilised aq. compsns. of gamma- *interferon* provide 2-30 doses - for repeated admin. in the treatment of e.g. renal cell carcinoma..
DC B04 P33 P34
IN NGUYEN, T
PA (GETH) GENENTECH INC
CYC 31
PI WO 9426302 A1 941124 (9501)* EN 21 pp
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE
W: AU CA CN CZ FI HU JP KR NO NZ PL SK
AU 9467822 A 941212 (9521)
FI 9505136 A 951027 (9603)
NO 9504544 A 951110 (9605)

ZA 9402955 A 951227 (9605) 18 pp
EP 697887 A1 960228 (9613) EN
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
CZ 9502955 A3 960417 (9623)
TW 275585 A 960511 (9635)
JP 08510242 W 961029 (9705) 24 pp
SK 9501378 A3 970205 (9715)
ADT WO 9426302 A1 WO 94-US4928 940504; AU 9467822 A AU 94-67822 940504;
FI 9505136 A WO 94-US4928 940504, FI 95-5136 951027; NO 9504544 A WO
94-US4928 940504, NO 95-4544 951110; ZA 9402955 A ZA 94-2955 940428;
EP 697887 A1 EP 94-916004 940504, WO 94-US4928 940504; CZ 9502955 A3
CZ 95-2955 940504; TW 275585 A TW 94-104134 940506; JP 08510242 W JP
94-525522 940504, WO 94-US4928 940504; SK 9501378 A3 WO 94-US4928 940504, SK 95-1378 940504
FDT AU 9467822 A Based on WO 9426302; EP 697887 A1 Based on WO 9426302;
JP 08510242 W Based on WO 9426302
PRAI US 93-60327 930512
AB WO 9426302 A UPAB: 950110
Stable , aqueous compsns. (I) of non-lyophilised gamma *interferon* (*IFN* -gamma) comprise: (a) an acetate buffer to maintain *pH* between *4* . *0* and 6.0; (b) a non-ionic detergent; (c) an isotonifier ;and (d) a preservative selected from phenol, benzyl alcohol or benzenethonium halide. Also claimed are: (i) a container contg. (I); (ii) a method of stabilising *IFN* -gamma which comprises combining unlyophilised *IFN* -gamma with water according to steps (a) - (d); and (iii) a method for intrapulmonary admin. of *IFN* -gamma according to (ii).
USE - *IFN* -gamma is an antiviral and anti-proliferative agent useful in the treatment of e.g. atopic dermatitis and renal cell carcinoma. *IFN* -gamma is a 15 kD protein which is heat sensitive and prone to aggregation and proteolytic degradation. Commercial compsns. are non-stabilised single-dosage units, unsuitable for the prolonged treatment of the above conditions requiring repeated admin. (I) provides *stable* aq. solns. contg 2-30 doses with a specific activity for *IFN* -gamma of 2 x 10-7 U/mg (claimed) which can be stored at 2-8 deg.C at most 2 weeks. (I) may also be used to treat infections associated with severe injury e.g. pneumonia, major wound infection. Admin. is by injection (i.v., i.p., or i.m.) or as an aerosol suitable for intranasal or intrapulmonary delivery. Dosage is 0.001-1.0 (pref. 0.01-0.1) mg/kg.
Dwg.0/0

L51 ANSWER 4 OF 20 MEDLINE DUPLICATE 1
AN 91199100 MEDLINE
TI Two discrete types of tumor necrosis factor-resistant cells derived from the same cell line.
AU Vanhaesebroeck B; Van Bladel S; Lenaerts A; Suffys P; Beyaert R; Lucas R; Van Roy F; Fiers W
CS Laboratory of Molecular Biology, State University, Gent, Belgium.
SO CANCER RESEARCH, (1991 May 1) 51 (9) 2469-77.
Journal code: CNF. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 9107
AB From the murine fibrosarcoma cell line L929s, which is sensitive to tumor necrosis factor (TNF)-mediated cell lysis, two discrete types of TNF-resistant variants were derived by TNF selection. Cells of the first type (named L929r1) were not sensitized to TNF cytotoxicity by cotreatment with either inhibitors of protein or RNA synthesis, or gamma- *interferon* , despite the presence of a functional gamma- *interferon* response. L929r1 constitutively produced TNF in the supernatant and expressed membrane-bound TNF, which was not bound to the TNF receptor. In fact, TNF receptors could not be demonstrated on L929r1 cells, not even after *low* *pH* treatment and/or incubation with antiserum to TNF. L929r1 exhibited a *stable* TNF-resistant phenotype in the absence of further TNF selection. No evidence could be obtained that TNF acted as an autocrine growth factor for these cells. L929r2, the second type of TNF-resistant L929 cells, became sensitive to TNF lysis in the presence of RNA or protein synthesis inhibitors, or in the presence of gamma- *interferon* . TNF induced the secretion of interleukin 6 in these cells, additionally showing that functional TNF signaling in these cells indeed takes place, but does not lead to cell lysis under normal conditions. L929r2 did not produce TNF, also not upon stimulation with exogenous TNF. The number and binding affinity of TNF receptors were not consistently different between L929s and L929r2 cells. In the absence of further TNF selection, L929r2 gradually reverted to TNF sensitivity. This sensitivity was not reversible to TNF resistance by the gene-regulatory agents 5-azacytidine or sodium butyrate. Treatment with these agents also did not affect the TNF sensitivity of L929s cells nor the TNF resistance of L929r1 and L929r2 cells. In summary, our results suggest the existence among cells of the same cell line of discrete mechanisms for acquisition of resistance to TNF-mediated cell lysis.

L51 ANSWER 5 OF 20 MEDLINE DUPLICATE 2
AN 91100022 MEDLINE
TI Mechanism for candidacidal activity in macrophages activated by recombinant gamma *interferon* .
AU Watanabe K; Kagaya K; Yamada T; Fukazawa Y
CS Department of Microbiology, Yamanashi Medical College, Japan..
SO INFECTION AND IMMUNITY, (1991 Feb) 59 (2) 521-8.
Journal code: GO7. ISSN: 0019-9567.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 9104
AB Candidacidal activity in macrophages activated by recombinant gamma *interferon* was examined kinetically in relation to acidification of phagolysosomes. In resident peritoneal macrophages (PMPs) of BALB/c mice, enhanced killing activity against Candida albicans was demonstrated after incubation with 100 U of gamma *interferon* per ml for 24 h but not after incubation for 48 to 72 h. Conversely, increased generation of H_2O_2 was exhibited in PMPs incubated from 48 to 72 h but not in PMPs incubated for 24 h. In normal PMPs, fusion of lysosomes to candida-containing phagosomes was readily accomplished and phagosome-lysosome fusion was not enhanced further by activation. The candidacidal substance was extracted from granule-rich fractions of either normal or activated PMPs by using citric acid (pH 2.7) in equal amounts; the substance showed a noncationic, heat- *stable* protein nature. In addition, when phagolysosomal pH was determined by flow cytometry of intraphagolysosomal fluorescein isothiocyanate-labeled C. albicans, phagolysosomes with *low* *pH* (less than *4* . *0*) were detected in about 40% of PMPs activated for 24 h but not in those activated for 72 h or in normal PMPs. Moreover, increasing the intralysosomal pH with NH4Cl resulted in a significant reduction of candidacidal activity in activated PMPs. These results indicate that the candidacidal activity of gamma *interferon* -activated PMPs correlates well with enhanced acidification of their phagolysosomes and suggest that the candidacidal activity of activated PMPs is independent from reactive oxygen molecules and is mediated by proteinaceous substance(s) generated only in a strong acidic milieu of phagolysosomes by activation.

L51 ANSWER 6 OF 20 CA COPYRIGHT 1997 ACS DUPLICATE 3
AN 112:84197 CA
TI *Low* *pH* pharmaceutical compositions of recombinant beta- *interferon*
IN Hershenson, Susan I.; Thomson, Jody
PA Cetus Corp., USA
SO PCT Int. Appl., 35 pp.
CODEN: PIXXD2
PI WO 8905158 A1 890615
DS W: AU, DK, FI, JP, NO
RW: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE
AI WO 88-US4307 881202
PRAI US 87-131375 871210
DT Patent

LA English
AB A *stable* parenteral compn. having pH of 2-4 comprises a recombinant *interferon* -.beta. (*IFN* -.beta.) dissolved in an inert carrier contg. glycerol or polyethylene glycol (mol. wt. 190-1600) as a stabilizer/solubilizer. The strain of *IFN* -.beta.ser17-producing Escherichia coli carrying plasmid -pSY2501 was cultured; the cells were disrupted and extd. with 2-butanol; the ext. was purified by centrifugation, precolumn chromatog., ultrafiltration, and column chromatog.; the final supernatant was then stabilized by adding either 25% glycerol or 25% PEG-300. The formulations remained sol. after 1 wk storage at 4.degree.. Cytopathic effect assay results showed the formulations maintained bioactivity at 4.degree. during 1 wk.

L51 ANSWER 7 OF 20 CA COPYRIGHT 1997 ACS
AN 110:179532 CA
TI Pharmaceutical injections containing recombinant beta-interferons and nonionic surfactants and sugars as stabilizers
IN Shaked, Zeev; Stewart, Tracy; Thomson, Jody; Thomson, James William; Taforo, Terrance; Hershenson, Susan
PA Cetus Corp., USA
SO Eur. Pat. Appl., 83 pp.
CODEN: EPXXDW
PI EP 270799 A1 880615
DS R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE
AI EP 87-115693 871026
PRAI US 86-923423 861027
DT Patent
LA English
AB A *stable* pharmaceutical compn. for parenteral administration comprises a recombinant *interferon* -.beta. (*IFN* -.beta.) protein dissolved in an inert carrier medium contg. .gtoreq.1 biocompatible nonionic polymeric detergent(s) as a solubilizer or stabilizer. The strain of *IFN* -.beta.ser17-producing E. coli carrying plasmid pSY2501 was cultured. The refractile bodies contg. *IFN* -.beta.ser17 protein were harvested, concd., and disrupted; EDTA was added to kill residual bacterial and sucrose was added to create a concn. gradient of 1.1-1.25 g/mL and the soln. was centrifuged. The pellet was solubilized in phosphate-buffered saline with 2% Na dodecyl sulfate and dithiothreitol and extd. with 2-butanol. The ext. was again mixed with 0.1% Na dodecyl sulfate in phosphate-buffered saline and dithiothreitol; the mixt. was centrifuged and the pellet contained 81% *IFN* -.beta.. The pellet was then processed by Sephacryl S200 pre-column chromatog., oxidized by o-iodobenzoic acid, concd., and purified by Sephadex G-75 column. The desalting step was performed at pH 9.2 with Sephadex G-25 column equilibrated with 0.1% Na laurate and the pH of the eluate was lowered to *pH* *3* *0* to ppt. the Na laurate. The mixt. was centrifuged and the supernatant was stabilized by adding 0.15% Trycol LAL-12; the pH was raised to .apprx.7.0 with NaOH and 5g dextrose was then added; finally the soln. was sterile-filtered and the dosage amts. of *IFN* -.beta.ser17 (0.25 mg) were filled into vials and frozen to between -35 and -45.degree.. A preferred lyophilized normal dose formulation comprises recombinant *IFN* -.beta. 0.25 mg/mL, polyoxyethylene lauryl ether 0.15% by vol., Na phosphate buffer 20 mM, dextrose 0.2%, and mannitol 2%. These *IFN* -.beta. formulations are at least as *stable* as human serum albumin-contg. formulations and they do not require strong solubilizing agents such as SDS.

L51 ANSWER 8 OF 20 MEDLINE DUPLICATE 4
AN 88116691 MEDLINE
TI Spontaneous *interferon* production by pulmonary leukocytes is associated with lentivirus-induced lymphoid interstitial pneumonia.
AU Lairmore M D; Butera S T; Callahan G N; DeMartini J C
CS Department of Pathology, College of Veterinary Medicine and Biomedical Sciences, Fort Collins, CO 80523..
SO JOURNAL OF IMMUNOLOGY, (1988 Feb 1) 140 (3) 779-85.
Journal code: IFB. ISSN: 0022-1767.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 8805
AB Ovine lentiviruses share genome sequence, structural features, and replicative mechanisms with HIV, the etiologic agent of AIDS. A lamb model of lentivirus-induced lymphoid interstitial pneumonia, comparable to lymphoid interstitial pneumonia associated with pediatric AIDS, was used to investigate production of leukocyte-soluble mediators. Lentivirus-infected lambs and adult sheep with severe lymphoid interstitial pneumonia had significantly elevated levels of spontaneous *interferon* (*IFN*) production from pulmonary leukocytes compared with ovine lentiviruses-infected animals with mild or no lesions of lymphoid interstitial pneumonia or non-infected controls. However, peripheral blood mononuclear cells from lentivirus-infected lambs did not spontaneously release significant amounts of *IFN* . *IFN* production by pulmonary lymph node lymphocytes was enhanced in the presence of lentivirus-infected alveolar macrophages. Animals with lentivirus-induced disease and spontaneous *IFN* production had enhanced virus replication within tissues. The ovine lentiviruses-induced *IFN* had a m.w. of between 25,000 and 35,000 and was resistant to freeze/thawing procedures. The *IFN* activity was sensitive to trypsin and *stable* to *low* *pH* and heat. *IFN* with similar physical and biochemical properties was produced when ovine lentiviruses was added to control leukocyte cultures. IL-2 and PGE2 production and responses to mitogen by pulmonary lymph node lymphocytes of lentivirus-diseased lambs were not statistically different from control animals. Increased local production of *IFN* in lentivirus-infected host tissues may serve to accelerate the entry of leukocytes into virus-induced lesions promoting cell-mediated tissue damage and also provide increased numbers of cells for virus replication.

L51 ANSWER 9 OF 20 MEDLINE DUPLICATE 5
AN 89092415 MEDLINE
TI A T-lymphocyte-derived factor that enhances IgG-dependent release of leukotriene B4 (LTB4) from human neutrophils.
AU Tsai J J; Maestrelli P; Cromwell O; Moqbel R; Fitzharris P; Kay A B
CS Department of Allergy and Clinical Immunology, National Heart and Lung Institute, London, U.K..
SO IMMUNOLOGY, (1988 Nov) 65 (3) 449-56.
Journal code: GH7. ISSN: 0019-2805.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 8904
AB We describe a human blood mononuclear cell (MNC)-derived leukotriene release enhancing factor (LREF) which significantly increased IgG-dependent leukotriene B4 (LTB4) generation by neutrophils. MNCs incubated with phytohaemagglutinin (PHA) or anti-CD3 monoclonal antibody and PHA-stimulated ER+ lymphocytes produced a 150-350% increase in LTB4 generation from IgG-stimulated neutrophils. With PHA, maximal activity was observed 48 hr after culture in serum-free medium. LREF was relatively *stable* when exposed to *low* *pH* (pH 2) or heat (56 degrees, 60 min). Following progressive purification by gel filtration (FPLC, Superose 12) and chromatofocusing (FPLC, Mono P) LREF was associated with proteins of molecular weight of 35-40 kD and a pI of 5.1-5.5. Partially purified LREF did not contain detectable amounts of interleukin 2 (IL-2) or *interferon* -gamma (*IFN* -gamma). Although high concentrations of recombinant granulocyte-macrophage colony stimulating factor (rGM-CSF) (greater than 2 ng/ml) and recombinant tumour necrosis factor (rTNF) (greater than 100 U/ml) gave a slight (60%) enhancement of LTB4 generation, this was considerably less than that of partially purified LREF (350%). Our results suggest that human lymphocyte-derived LREF may play a role in the amplification of inflammatory reactions involving sensitized lymphocytes, neutrophils and lipid mediators.

L51 ANSWER 10 OF 20 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 6
AN 89:274944 BIOSIS
DN BA88:11026
TI PRODUCTION AND SOME PROPERTIES OF PORCINE SPLEEN *INTERFERON*
AU LIU H; YANG X-L
CS WUHAN INST. VIROL., ACAD. SINICA, WUHAN.

SO VIROL SIN 3 (4). 1988. 389-394. CODEN: BIZAES
LA Chinese
AB Porcine spleen cells induced with Newcastle disease virus F strain could produce an antiviral substance. The substance was sensitive to trypsin and did not penetrate the dialyser. These indicated that it was characteristic of an *Interferon* . The antiviral activity of crude porcine spleen cell *interferon* (PSIFN) was 1.3 .times. 105u/ml on porcine kidney cells. PSIFN production was significantly enhanced by pretreating cells with porcine *IFN* . The crude PSIFN was less *stable* to *low* *pH* treatment, to 56.degree.C and to 0.1% SDS. In addition, the antiviral activity of PSIFN was 17-fold higher when measured on human cells than on homologous cells. The titer of PSIFN was 3.2 .times. 103u/ml on rabbit kidney cells and was 1.15 .times. 103u/ml on mouse cells.

L51 ANSWER 11 OF 20 MEDLINE DUPLICATE 7
AN 87167638 MEDLINE
TI Characterization of regulatory (*interferon* -alpha/beta) and accessory (LAF/IL 1) monokine activities from liver granuloma macrophages of Schistosoma mansoni-infected mice.
AU Elliott D E; Righthand V F; Boros D L
NC AI-12913 (NIAID)
CA-09304 (NCI)
SO JOURNAL OF IMMUNOLOGY, (1987 Apr 15) 138 (8) 2653-62. Journal code: IFB. ISSN: 0022-1767.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 8707
AB Previously it was shown that macrophages (M phi) isolated from the vigorous (Vig) or modulated (Mod) liver granulomas (Gr) of Schistosoma mansoni-infected mice restored mitogen and parasite egg antigen-induced proliferative responses to accessory cell-depleted lymphocytes. Furthermore, supraoptimal concentrations of highly activated VigGrM phi suppressed lymphoproliferation to a greater extent than did the lesser activated ModGrM phi. In this study we investigated the role of soluble mediators in GrM phi accessory/regulatory activity. Indomethacin released VigGrM phi-mediated inhibition of mitogen but not antigen-induced lymphoproliferation. Extensively dialyzed serum-free GrM phi culture supernatant nonspecifically suppressed SEA- or KLH-induced blastogenesis. Culture supernatants also reduced vesicular stomatitis virus-induced plaque formation in supernatant-pretreated L-929 fibroblasts. The 20 to 45 Kd GrM phi-derived lymphoproliferation suppressive factor (SF) and the 20 to 50 Kd viral plaque-reducing factor (PRF) were *stable* at *low* *pH* , but became inactivated by heat and trypsin digestion. Although freshly isolated Vig or ModGrM phi contained preformed SF and PRF, in vitro production of the factors were depressed by protein synthesis inhibitors. Moreover, SF was active only when added to cultures before day 3 of the 6-day proliferation assay. Both SF and PRF were specifically retained on rabbit anti-murine *IFN* -alpha/beta immunoaffinity columns. Thus, the suppressive activity of Vig or ModGrM phi is in part mediated by a monokine that shares physical, biological, and antigenic characteristics with murine *IFN* -alpha/beta. In contrast to the suppression of antigen-driven proliferation, GrM phi culture supernatant costimulated PHA-induced mitogenesis. The 13 to 21 Kd GrM phi-derived lymphocyte-activating factor (LAF) was *stable* to heat, *low* *pH* , and trypsin digestion. Freshly isolated Vig or ModGrM phi contained preformed LAF, although its in vitro production was depressed by protein synthesis inhibitors. The physical and biological characteristics of GrM phi-derived LAF appear similar to IL 1. It is concluded that both Vig and ModGrM phi secrete regulatory/accessory monokines that may contribute to the initiation and maintenance of the focal inflammatory granulomatous response.

L51 ANSWER 12 OF 20 CA COPYRIGHT 1997 ACS DUPLICATE 8
AN 106:23257 CA
TI *Stable* gamma *interferon* formulation
IN Yim, Zachary; Chaudry, Imtiaz Ahmad
PA Schering Corp., USA
SO Eur. Pat. Appl., 12 pp.
CODEN: EPXXDW
PI EP 196203 A2 861001
DS R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE
AI EP 86-302104 860321
PRAI US 85-715851 850325
US 85-740932 850603
DT Patent
LA English
AB A biol. *stable* lyophilized .gamma.- *interferon* formulation contains .gamma.- *interferon* and a compatible buffer to maintain *pH* *4* . *0* -6.0 when reconstituted with water to 0.001-10 mg .gamma.- *interferon* /mL. Thus, the following ingredients were mixed and the soln. lyophilized: .gamma.- *interferon* 0.5, aminoacetic acid 20, anhyd. citric acid 1.5, NaH2PO4 1.8, Na2EDTA 0.1, ascorbic acid 2, cysteine-HCl 0.75, human serum albumin 1, NaOH (0.1N) q.s. to pH 4.5 mg/vial; for injection, water is added to 1 mL.

L51 ANSWER 13 OF 20 WPIDS COPYRIGHT 1997 DERWENT INFORMATION LTD
AN 86-157521 [25] WPIDS
DNC C86-067282
TI New lymphokine, LK 2 and monoclonal antibodies - for treating tumours.
DC B04 D16
IN KURIMOTO, M; MITSUHASHI, M
PA (HAYB) HAYASHIBARA SEIBUTSU KAGAKU; (HAYB) HAYASHIBARA KEN; (HAYB) HAYASHIBARA SEIBUTS; (HAYB) HAYASHIBARA BIOCHEMICAL LAB; (HAYB) HAYASHIBARA SEIBUTSU KAGAKU RES CO LTD
CYC 12
PI GB 2168355 A 860618 (8625)* 16 pp
FR 2572936 A 860516 (8626)
AU 8549708 A 860515 (8627)
SE 8505286 A 860510 (8627)
JP 61115026 A 860602 (8628)
JP 61115027 A 860602 (8628)
JP 61115028 A 860602 (8628)
JP 61115099 A 860602 (8628)
DE 3539775 A 861106 (8646)
ES 8703161 A 870416 (8719)
CH 664574 A 880315 (8816)
ES 8801582 A 880416 (8823)
GB 2168355 B 890419 (8916)
IT 1184668 B 871028 (9041)
US 5003048 A 910326 (9115)
US 5019385 A 910528 (9124)
US 5030564 A 910709 (9130)
AT 8503276 A 920115 (9206)
SE 468853 B 930329 (9315)
JP 05023755 B 930405 (9316) 11 pp
JP 05032033 B 930514 (9322) 9 pp
DE 3539775 C2 940526 (9419) 19 pp
KR 9304596 B1 930601 (9423)
JP 08011759 B2 960207 (9610) 10 pp
ADT GB 2168355 A GB 85-27466 851107; FR 2572936 A FR 85-16536 851108; JP 61115026 A JP 84-28396 841109; JP 61115027 A JP 84-236356 841109; JP 61115028 A JP 85-166754 850730; JP 61115099 A JP 84-236357 841109; DE 3539775 A DE 85-3539775 851109; ES 8703161 A ES 85-548727 851108; ES 8801582 A ES 86-556785 860625; US 5003048 A US 88-223717 880721; US 5019385 A US 85-792158 851028; US 5030564 A US 88-223719 880721; SE 468853 B SE 85-5286 851108; JP 05023755 B Div ex JP 84-236356 841109, JP 85-28396 841109; JP 05032033 B JP 84-236357 841109; DE 3539775 C2 DE 85-3539775 851109; KR 9304596 B1 KR 85-8229 851105; JP 08011759 B2 JP 84-236356 841109
FDT JP 05023755 B Based on JP 61115026; JP 05032033 B Based on JP 61115099; JP 08011759 B2 Based on JP 61115027
PRAI JP 84-236356 841109; JP 84-236357 841109; JP 85-28396 850218; JP 85-166754 850730
AB GB 2168355 A UPAB: 931112
Lymphokine (LK2) with the following physicochemical properties is new: (1) mol.wt.: 20000+-2000 daltons; (2) isoelectric pt.:

pI=6.2+-0.3; (3) electrophoretic mobility: on Disc-PAGE, Rf=0.29(+-)0.02; (4) UV absorption spectrum: absorption maximum at 280 nm; (5) solubility in solvents: soluble in water, saline and phosphate buffer; scarcely soluble or insoluble in ethyl ether, ethyl acetate or chloroform; (6) colouring reaction: protein-positive by Lowry's method or microburet method; saccharide-positive by the phenol-sulphuric acid method or anthrone-sulphuric acid method; (7) biological activities: cytotoxic on L 929 cells and KB cells; free from *interferon* activity; (8) stability in aq. soln. *stable* up to 60 deg.C when incubated at pH 7.2 for 30 mins; *stable* oVer a *pH* range of *4* . *0* -11.0 when incubated at 4 deg.C for 16 hrs.; (9) stability on cryopreservation: *stable* at -10 deg.C over a period of one month or longer.
Prodn. of LK 2 by induction of human cells, and monoclonal antibodies to LK2 and their prodn. are also claimed, as is purificn. of LK2 by affinity, chromatography.
USE - LK2 shows cytotoxic activity against malignant tumour cells. LK2 may also be used to enhance antioncotic effects of chemotherapeutic agents, roadening their tumour sepctra, as well as enabling treatment of drug-resistant tumours. The monoclonal antibodies may be used as a ligand for affinity chromatography directed to LK2 prodn., as well as in diagnosis of a variety of human diseases because of their specificity to LK2 which damages malignant tumours. Dosage is 5-5 x 10 power8 units/day.
Dwg.0/0

L51 ANSWER 14 OF 20 BIOSIS COPYRIGHT 1997 BIOSIS DUPLICATE 9
AN 86:455330 BIOSIS
DN BA82:112172
TI *INTERFERON* PRODUCTION IN HUMAN BLOOD CELL CULTURES STIMULATED BY NOCARDIA-RUBRA.
AU MA L; WANG C-M; ET AL
CS LIAONING INST. BASIC MED. SCI., SHENYANG.
SO CHIN J MICROBIOL IMMUNOL (BEIJING) 6 (3). 1986. 168-170.
CODEN:
ZWMZDP ISSN: 0254-5101
LA Chinese
AB Heat-killed preparations of Nocardia rubra (NR) have been demonstrated to induce *interferon* (*IFN*) in cultures of normal adult human whole blood cells and mononuclear cells. The maximum *IFN* response was observed in 24 hr after initiation of culture at a final NR concentration of 50-200.mu.g/ml. The type of *IFN* induced by NR is similar to *IFN* -.alpha., because it was *stable* to *low* *pH* and heat. The T cell or B cell cultures stimulated by NR failed to produce *IFN* . The whole blood cultures stimulated by the cell wall skeleton of NR (NR-CWS) failed to produce *IFN* either.

L51 ANSWER 15 OF 20 WPIDS COPYRIGHT 1997 DERWENT INFORMATION LTD
AN 85-179316 [30] WPIDS
DNC C85-078104
TI New antitumour human lymphokine LK1 - and derived monoclonal antibodies used for purificn. and diagnosis.
DC B04 D16
IN KURIMOTO, M; MITSUHASHI, M
PA (HAYB) HAYASHIBARA SEIBUTSU KAGAKU
CYC 10
PI FR 2556220 A 850614 (8530)* 33 pp
JP 60126222 A 850705 (8533)
JP 60126228 A 850705 (8533)
GB 2153364 A 850821 (8534)
JP 60142926 A 850729 (8536)
GB 2153364 B 870923 (8738)
CH 664969 A 880415 (8820)
US 4758549 A 880719 (8831)
IT 1199239 B 881230 (9116)
JP 05026468 B 930416 (9318) 8 pp
JP 05027640 B 930421 (9319) 12 pp
JP 05032032 B 930514 (9322) 9 pp
KR 9300188 B1 930111 (9416)
ADT FR 2556220 A FR 84-18868 841211; JP 60126222 A JP 84-10941 841210; JP 60126228 A JP 83-233570 831213; GB 2153364 A GB 84-31152 841210; JP 60142926 A JP 83-244598 831227; US 4758549 A US 84-675291 841127; JP 05026468 B Div ex JP 83-233570 831213, JP 84-10941 831213; JP 05027640 B JP 83-233570 831213; JP 05032032 B JP 83-244598 831227; KR 9300188 B1 KR 84-7900 841213
FDT JP 05026468 B Based on JP 60126222; JP 05027640 B Based on JP 60126228; JP 05032032 B Based on JP 60142926
PRAI JP 83-233570 831213; JP 83-244598 831227
AB FR 2556220 A UPAB: 930925
New human lymphokine (LK1) which is cytotoxic towards malignant tumour cells has the following characteristics: (1) mol. wt. 18000-22000; (2) isoelectric point 5.4-5.8; (3) electrophoretic mobility (polyacrylamide gel) Rf 0.27-0.31; (4) UV absorption max. at about 280 nm; (5) soluble in water, physiological serum and phosphate buffer but only sparingly soluble in Et2O, Et acetate and chloroform; (6) positive for protein in the Lowry and microburette tests and for sugar in the H2SO4-phenol and H2SO4-anthrone tests; (7) cytotoxic for L929 cells, inhibits growth of KB cells and has practically no *interferon* activity; (8) is *stable* at up to 60 deg. C when incubated at pH 7.2 for 30 min. and at pH 4-11 when incubated at 4 deg. C for 1 lbr, and (9) is *stable* for 1 month or more at -10 deg. C.
USE - LK1 is useful as an antitumour agent and has no damaging effects on normal cells. It can also be used to raise antibodies (Ab) which are useful (1) for affinity purification of LK1 and (2) as diagnostic reagents.
0/0

L51 ANSWER 16 OF 20 MEDLINE
AN 83093735 MEDLINE
TI Control of the *interferon* system: an inhibitor of *interferon* action.
AU Lefkowitz E J; Fleischmann W R Jr
NC 5RO1 CA 26475 (NCI)
5S 07 RR-05427 (NCRR)
SO TEXAS REPORTS ON BIOLOGY AND MEDICINE, (1981-82) 41 317-23.
Journal code: VNN. ISSN: 0040-4675.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 8304
AB An inhibitor of *interferon* action has been identified which is present in *IFN* -gamma preparations. The inhibitor is produced following rising *interferon* concentrations in mitogen stimulated mouse spleen cell cultures. Indications are that the inhibitor is produced in response to the production of *interferon* , and may therefore be a feedback control mechanism for the *interferon* system. The action of the inhibitor is independent of both *interferon* type and concentration, and seems to act by preventing the establishment of the *interferon* -induced antiviral state at some point following the interaction of the *interferon* molecule with the cell membrane. The inhibitor has an apparent molecular weight of 8,000 to 10,000 daltons and is *stable* to treatment with *low* *pH* , heat, and trypsin. It is proposed that the inhibitor has the specific role in vivo of controlling *interferon* -mediated activities.

L51 ANSWER 17 OF 20 MEDLINE DUPLICATE 10
AN 79079857 MEDLINE
TI Thermal and vortical stability of purified human fibroblast *interferon* .
AU Sedmak J J; Jameson P; Grossberg S E
SO ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY, (1978) 110 133-52.
Journal code: 2LU. ISSN: 0065-2598.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 7904
AB The loss of biological activity upon heating or agitation of human interferons is markedly altered by changing their aqueous environment. *Low* *pH* significantly stabilizes liquid fibroblast *interferon* at 68 degrees C and 37 degrees C whereas chaotropic salts stabilize at 68 degrees C but not

at 37 degrees C; this anomalous result may be due to reactivation of biological activity at the higher temperature. The concentration of extraneous proteins influences the apparent thermal stability at any temperature and pH; thus, *interferon* was not *stable* even at *low* *pH* at protein concentrations less than 5 microgram/ml. Solutions of partially purified fibroblast *interferon* can be inactivated by mechanical stress; the addition of proteins or nonionic detergents prevents such inactivation. Freeze-dried preparations show the greatest thermal stability. The use of high-temperature, accelerated storage tests makes it possible to predict the shelf-life of freeze-dried *interferon* .

L51 ANSWER 18 OF 20 MEDLINE
AN 79014993 MEDLINE
TI Stabilization of interferons.
AU Sedmak J J; Grossberg S E
SO TEXAS REPORTS ON BIOLOGY AND MEDICINE, (1977) 35 198-204.
Ref: 25
Journal code: VNN. ISSN: 0040-4675.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LA English
FS Priority Journals
EM 7901
AB It is now obvious that there are a number of factors which can influence the stability of interferons. Since human fibroblast *interferon* is especially unstable both to heat and mechanical stress, the use of stabilizing conditions such as *low* *pH* or thioctic acid should facilitate purification and concentration of this *interferon* . Leukocyte *interferon* , on the other hand, seems to be more *stable* even when highly purified; however, losses in activity can occur in very dilute solutions containing low concentrations of protein. Inactivation during storage of interferons may be avoided by using freeze-dried preparations. In order to generate large quantities of purified, *stable* interferons for clinical use, there is a need to establish an armamentarium of different nontoxic techniques and approaches that will enable investigators to stabilize human interferons at each step in preparation, processing, concentration, purification, shipment and storage.

L51 ANSWER 19 OF 20 MEDLINE DUPLICATE 11
AN 77167165 MEDLINE
TI Effect of chaotropic salts and protein denaturants on the thermal stability of mouse fibroblast *interferon* .
AU Jariwalla R J; Grossberg S E; Sedmak J J
SO JOURNAL OF GENERAL VIROLOGY, (1977 Apr) 35 (1) 45-52.
Journal code: I9B. ISSN: 0022-1317.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 7708
AB Altering the aqueous environment, especially with agents that affect hydrogen bonds, markedly affects the stability of mouse L cell *interferon* . *Low* *pH* stabilizes *interferon* whereas high pH labilizes it; heavy water further enhances *interferon* thermostability at pH 2 but not at pH 9. Exposure to the protein denaturants, 4 M-guanidine hydrochloride and 6 M-urea, significantly decreases the activity of *interferon* at pH 2 and pH9; however, the residual *interferon* activity is relatively thermostable. Certain chaotropic salts protect *interferon* against thermal destruction, and in terms of effectiveness, their sequence is in the order SCN- greater than I- larger than or equal to Cl- = ClO4- - Br- greater than NO3-. *Interferon* becomes more *stable* to heat as the NaSCN concentration is increased from 0-25 M to 2-0 M. Molecular sieve chromatography of *interferon* in the presence of 1-5 M-NaSCN at pH 7 shows a shift in its apparent mol. wt. from 25000 to 42000. Unlike most proteins, the unfolded conformation of *interferon* appears to be more *stable* to heat than the molecule with a smaller Stokes' radius.

L51 ANSWER 20 OF 20 MEDLINE DUPLICATE 12
AN 76111461 MEDLINE
TI The influence of physicochemical factors on the thermal inactivation of murine *interferon* .
AU Jariwalla R; Grossberg S E; Sedmak J J
SO ARCHIVES OF VIROLOGY, (1975) 49 (2-3) 261-72.
Journal code: 8L7.
CY Austria
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 7605
AB The degradation of biological activity of virus-induced murine *interferon* was determined in linear nonisothermal and multiple isothermal tests. The stabilizing effect of pH during heating on *interferon* in solution was greatest at *low* *pH* , such that pH 2 greater than pH 5 greater than pH 7 greater than or equal to pH 9; freeze-dried preparations of *interferon* were also more heat- *stable* at acid pH than at neutral pH. Heat stability was a function of the H+-ion concentration rather than the ionic composition of the buffer; *interferon* solutions containing monovalent cations with different ionic radii had similar heat stability. A change in the H+ ion concentration was a critical event during the cooling of heated *interferon* : a shift in the direction of acidity contributed to stability whereas a shift towards alkalinity led to inactivation. The rate of cooling of heated *interferon* significantly influenced its residual activity. Rapid cooling and sudden freezing decreased the residual activities of interferons at pH 2 and 9 more than "normal" cooling, an effect not observed at pH 7. *Interferon* heated to 80degree C could not be reactivated at 40degree C or 55degree C. *Interferon* of higher apparent molecular weight was more heat- *stable* than that with lower apparent molecular weight. It is postulated that the physicochemical alterations in the aqueous environment significantly affecting the stability of *interferon* operate by producing changes in the size and/or conformation of *interferon* molecules. A model is proposed that relates thermal inactivation to different possible molecular states of *interferon* .

=> d his (FILE 'HOME' ENTERED AT 16:02:23 ON 03 MAY 1997)
FILE 'MEDLINE, BIOSIS, CA, WPIDS, JICST-EPLUS' ENTERED AT 16:02:55
ON 03 MAY 1997
L1 2514 FILE MEDLINE
L2 3034 FILE BIOSIS
L3 2344 FILE CA
L4 151 FILE WPIDS
L5 494 FILE JICST-EPLUS
TOTAL FOR ALL FILES
L6 8537 S (IFN OR INTERFERON) (W) BETA
L7 6911 FILE MEDLINE
L8 12731 FILE BIOSIS
L9 29241 FILE CA
L10 4914 FILE WPIDS
L11 927 FILE JICST-EPLUS
TOTAL FOR ALL FILES
L12 54724 S (LOW PH) OR (PH (3A) (3.0 OR 4.0))
L13 1 FILE MEDLINE
L14 3 FILE BIOSIS
L15 8 FILE CA
L16 3 FILE WPIDS
L17 0 FILE JICST-EPLUS
TOTAL FOR ALL FILES
L18 15 S L6 AND L12
L19 11 DUP REM L18 (4 DUPLICATES REMOVED)
L20 45 FILE MEDLINE
L21 48 FILE BIOSIS
L22 68 FILE CA
L23 22 FILE WPIDS
L24 0 FILE JICST-EPLUS
TOTAL FOR ALL FILES
L25 183 S (IFN OR INTERFERON) AND L12
L26 0 FILE MEDLINE
L27 0 FILE BIOSIS

L28 1 FILE CA
L29 0 FILE WPIDS
L30 0 FILE JICST-EPLUS
TOTAL FOR ALL FILES
L31 1 S L25 AND MANNITOL AND ALBUMIN
L32 0 FILE MEDLINE
L33 1 FILE BIOSIS
L34 6 FILE CA
L35 2 FILE WPIDS
L36 0 FILE JICST-EPLUS
TOTAL FOR ALL FILES
L37 9 S L25 AND (MANNITOL OR ALBUMIN)
L38 0 FILE MEDLINE
L39 0 FILE BIOSIS
L40 0 FILE CA
L41 0 FILE WPIDS
L42 0 FILE JICST-EPLUS
TOTAL FOR ALL FILES
L43 0 S L37 NOT L9
L44 110 DUP REM L25 (73 DUPLICATES REMOVED)
L45 10 FILE MEDLINE
L46 8 FILE BIOSIS
L47 11 FILE CA
L48 6 FILE WPIDS
L49 0 FILE JICST-EPLUS
TOTAL FOR ALL FILES
L50 35 S L25 AND STABL?
L51 20 DUP REM L50 (15 DUPLICATES REMOVED)
=> d his (FILE 'HOME' ENTERED AT 16:02:23 ON 03 MAY 1997)
FILE 'MEDLINE, BIOSIS, CA, WPIDS, JICST-EPLUS' ENTERED AT 16:02:55
ON 03 MAY 1997
L1 2514 FILE MEDLINE
L2 3034 FILE BIOSIS
L3 2344 FILE CA
L4 151 FILE WPIDS
L5 494 FILE JICST-EPLUS
TOTAL FOR ALL FILES
L6 8537 S (IFN OR INTERFERON) (W) BETA
L7 6911 FILE MEDLINE
L8 12731 FILE BIOSIS
L9 29241 FILE CA
L10 4914 FILE WPIDS
L11 927 FILE JICST-EPLUS
TOTAL FOR ALL FILES
L12 54724 S (LOW PH) OR (PH (3A) (3.0 OR 4.0))
L13 1 FILE MEDLINE
L14 3 FILE BIOSIS
L15 8 FILE CA
L16 3 FILE WPIDS
L17 0 FILE JICST-EPLUS
TOTAL FOR ALL FILES
L18 15 S L6 AND L12
L19 11 DUP REM L18 (4 DUPLICATES REMOVED)
L20 45 FILE MEDLINE
L21 48 FILE BIOSIS
L22 68 FILE CA
L23 22 FILE WPIDS
L24 0 FILE JICST-EPLUS
TOTAL FOR ALL FILES
L25 183 S (IFN OR INTERFERON) AND L12
L26 0 FILE MEDLINE
L27 0 FILE BIOSIS
L28 1 FILE CA
L29 0 FILE WPIDS
L30 0 FILE JICST-EPLUS
TOTAL FOR ALL FILES
L31 1 S L25 AND MANNITOL AND ALBUMIN
L32 0 FILE MEDLINE
L33 1 FILE BIOSIS
L34 6 FILE CA
L35 2 FILE WPIDS
L36 0 FILE JICST-EPLUS
TOTAL FOR ALL FILES
L37 9 S L25 AND (MANNITOL OR ALBUMIN)
L38 0 FILE MEDLINE
L39 0 FILE BIOSIS
L40 0 FILE CA
L41 0 FILE WPIDS
L42 0 FILE JICST-EPLUS
TOTAL FOR ALL FILES
L43 0 S L37 NOT L9
L44 110 DUP REM L25 (73 DUPLICATES REMOVED)
L45 10 FILE MEDLINE
L46 8 FILE BIOSIS
L47 11 FILE CA
L48 6 FILE WPIDS
L49 0 FILE JICST-EPLUS
TOTAL FOR ALL FILES
L50 35 S L25 AND STABL?
L51 20 DUP REM L50 (15 DUPLICATES REMOVED)
=> s l6 and (mannitol and albumin)
L52 0 FILE MEDLINE
L53 0 FILE BIOSIS
L54 7 FILE CA
L55 5 FILE WPIDS
L56 0 FILE JICST-EPLUS TOTAL FOR ALL FILES
L57 12 L6 AND (MANNITOL AND ALBUMIN)
=> dup rem l57
PROCESSING COMPLETED FOR L57
L58 9 DUP REM L57 (3 DUPLICATES REMOVED)
=> d 1-9 bib ab
L58 ANSWER 1 OF 9 CA COPYRIGHT 1997 ACS DUPLICATE 1
AN 124:97762 CA
TI Dry powder formulation of interferons
IN Platz, Robert M.; Kimura, Narinobu; Satoh, Oichiro; Foster, Linda C.
PA Inhale Therapeutic Systems, Inc., USA
SO PCT Int. Appl., 21 pp.
CODEN: PIXXD2
PI WO 9531479 A1 951123
DS W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TT, UA
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG
AI WO 95-US6008 950515
PRAI US 94-246034 940518
DT Patent
LA English
AB Spray-dried, interferon-based dry powder formulations, particularly of *interferon* -. *beta* ., are provided for treating conditions in humans that are responsive to treatment with interferons by pulmonary delivery. Spray drying produces stable, high-potency dry powder formulations of interferons. Thus, 100 mL 10 mM NaCl soln. contg. 7 .times. 104 IU interferon/mL, 150 mg *mannitol* /mL, and 2 mg human serum *albumin* /mL was spray dried (inlet temp. 100.degree., outlet temp. 60.degree., feed rate of soln. 4.3 mL/min) with 81% retention of interferon activity.
L58 ANSWER 2 OF 9 CA COPYRIGHT 1997 ACS
AN 119:125242 CA
TI Improved process for preparing micronized polypeptide drugs
IN Platz, Robert M.; Ip, Anna; Witham, Clyde L.
PA SRI International, USA
SO PCT Int. Appl., 16 pp.
CODEN: PIXXD2
PI WO 9313752 A1 930722
DS W: CA, JP
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
AI WO 93-US373 930120
PRAI US 92-823218 920121
DT Patent
LA English
AB Solid particle aerosol formulations of polypeptide drugs are prepd. by (1) lyophilizing drug solns. which contain milling stabilizers and (2) milling the lyophilized drug in a fluid energy mill using a pure inert gas, preferably N. Use of milling stabilizers in the soln. and the pure filtered gas in the milling step reduces insol.

contaminants and inactive fractions in the milled product. Micronization of *interferon* -. *beta* . with human serum *albumin* as a milling stabilizer is demonstrated.
L58 ANSWER 3 OF 9 WPIDS COPYRIGHT 1997 DERWENT INFORMATION LTD
AN 89-114255 [15] WPIDS
CR 88-162888 [24]
DNC C89-050575
TI Stabilised recombinant beta-interferon for parenteral use - dissolved in medium contg. biocompatible nonionic polymeric detergent as solubiliser- stabiliser.
DC A96 B04 C03 D16
IN HERSHENSON, S; SHAKED, Z; STEWART, T; TAFORO, T; THOMSON, J;
THOMSON, J W
PA (SCHD) SCHERING AG; (CETU) CETUS CORP
CYC 15
PI WO 8902750 A 890406 (8915)* EN 82 pp
RW: AT BE CH DE FR GB IT LU NL SE
W: AU DK JP NO
AU 8825351 A 890418 (8930)
US 5183746 A 930202 (9308) 26 pp
ADT WO 8902750 A WO 88-US3313 880926; US 5183746 A CIP of US 86-923423
861027, US 87-100679 870929
PRAI US 87-100679 870929
AB WO 8902750 A UPAB: 941010
A stable pharmaceutical compsn. suitable for parenteral administration to animals or humans is claimed comprising a recombinant *interferon* - *beta* (rIFB) protein dissolved in an inert carrier medium comprising as a solubiliser/stabiliser a biocompatible non-ionic polymeric detergent (I).
(I) may be e.g., ethoxylated fatty alcohol ethers and lauryl ether; octylphenoxy polyethoxy ethanol cpds.; modified oxyethylated or oxypropylated straight-chain alcohols; polyethylene glycol monooleate cpds.; polyoxyethylene sorbitan fatty acid esters; phenolic fatty alcohol ethers; and block copolymers of propylene oxide and ethylene oxide.
The compsn. may also contain an additional solubilising or stabilising agent such as glycerol. The compsn. may be lyophilised and reconstitutable and the carrier medium may also contain a buffer e.g., acetate or phosphate and a bulking/stabilising agent, e.g., dextrose or a combination of dextrose and *mannitol* or dextrose and human serum *albumin* or hum
CYC 1
PI US 4808523 A 890228 (8911)* 14 pp
ADT US 4808523 A US 84-669259 841107
PRAI US 84-669259 841107
AB US 4808523 A UPAB: 930923
A Chinese hamster ovary cell designated CHO-beta-(1)-5-9 and deposited with the Pasteur Institute under Order No. I-340 is claimed which is resistant to greater than 50 nM methotrexate comprising the selectable marker pSVDHFR and a pSEVEIF DNA molecule which contains a sequence encoding human fibroblast interferon *IFN* - *beta* -(1) fused 60bp downstream from the SV40 early start gene. The cell being capable of being cultured in a culture medium so as to constitutively express the sequence encoding IFN-beta1, produce an IFN-beta1 glycoprotein at yields greater than 50,000 units/10 power 6 cells/24 hrs. and secrete the IFN-beta1 glycoprotein into the culture medium.
also claimed is prods. of human IFN-beta1 with cells derived form the cell CHO-1-5-9, Pasteur Institute I-340 which comprises growing the cells on a suitable surface in Dulbecco's modified minimal essential medium contg. 150 microgram/ml proline and 1% FCS, maintaining the culture at 37 deg.C, replacing the medium every 24 hrs., collecting the medium that has been replaced, contacting the collected medium with the absorb Blue Sepharose (RTM) so as to retain the IFN-beta1, washing the absorbent contg. the IFN-beta1 with 1.5M K to remove proteins other than IFN-beta1, eluting the IFN beta1 with a 40% propylene glycol soln., concentrating the eluate 4 fold and reducing the propylene glycol concn. to 10% by ultrafiltration under mild pressure, purifying the concd. eluate by affinity chromatography with monoclonal antibodies (MAbs) prepd. against IFN-beta1 from human fibroblasts the antibodies being bound to agarose-polyacryl hydrazide, eluting the homogeneous IFN-beta1 bound to the MAbs by washing with 50mM citric acid-HCl, pH2. The homogeneous IFN-beta1 may be dialysed against acetate buffer, pH 3.5 and supplemented with a compsn. comprising human serum *albumin* fraction V, *mannitol* and PVP (1,000-50,000 Mr). .
0/4
L58 ANSWER 5 OF 9 CA COPYRIGHT 1997 ACS
AN 110:237165 CA
TI Antitumor pharmaceuticals containing interferons and dipyridamole
IN Suzuki, Nobuo; Takakubo, Yoshiaki
PA Boehringer Ingelheim International G.m.b.H., Fed. Rep. Ger.
SO Eur. Pat. Appl., 27 pp.
CODEN: EPXXDW
PI EP 295317 A1 881221
DS R: GB
AI EP 87-108708 870616
DT Patent
LA English
AB Dipyridamole (I) or its salt is used in the manuf. of a pharmaceutical capable of enhancing the antitumor effect of an interferon when administered to a patient who is being treated with the interferon. A lyophilizate contained recombinant human interferon-.gamma. (2 .times. 106 IU) 2, human serum *albumin* 10.000, NaCl 1.750, *mannitol* 40.000, polyoxyethylene sorbitan monooleate 0.300, succinic acid 2.36, 1N NaOH 36.26 mg, and H2O to 1.00 mL; this compn. was lyophilized and stoppered. An ampule contained I 10, tartaric acid 4, polyethylene glycol 100 mg, 1N HCl to pH 2.7, H2O to 2 mL. The lyophilizate above was . formulations and they do not require strong solubilizing agents such as SDS.
L58 ANSWER 7 OF 9 CA COPYRIGHT 1997 ACS DUPLICATE 2
AN 107:183557 CA
TI Improved formulation for recombinant .beta.-interferon with protein or sugar stabilizer
IN Hanisch, Wolfgang Helmut; Taforo, Terrance; Fernandes, Peter Michael
PA Cetus Corp., USA
SO Eur. Pat. Appl., 34 pp.
CODEN: EPXXDW
PI EP 215658 A2 870325
DS R: AT, BE, CH, DE, FR, GB, IT, LI, NL, SE
AI EP 86-307070 860912
PRAI US 85-775751 850913
DT Patent
LA English
AB Recombinant .beta.-human *interferon* (. *beta* .-HIFN) is dissolved in a non-toxic, inert, therapeutically compatible aq. carrier, at a pH of 2-4. The soln. contains a stabilizer for the .beta.-HIFN, particularly human plasma protein fraction, human serum *albumin* ; or *mannitol* .
This formulation results in very low sodium dodecyl sulfate levels. .beta.-Interferon 0.25 mg/mL was formulated using 2.5% plasma protein fraction at pH 3-4, incubated 15-45 min.; the pH was adjusted to 7.3-7.5. At this pH, the solns. were very clear. The use of 5.0% human serum *albumin* also gave clear solns., whereas 2.5% HSA resulted in slightly hazy solns.
L58 ANSWER 8 OF 9 CA COPYRIGHT 1997 ACS
AN 109:91122 CA
TI Combination cancer therapy using recombinant human interleukin-2 and *interferon* -. *beta* .
IN Rudolph, Alfred
PA Cetus Corp., USA
SO Eur. Pat. Appl., 8 pp.
CODEN: EPXXDW
PI EP 241242 A1 871014
DS R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE
AI EP 87-302945 870403
PRAI US 86-847509 860403
US 87-4108 870116
DT Patent
LA English
AB A compn. useful for the therapeutic or prophylactic treatment of cancer comprises a mixt. of *interferon* -. *beta* .

(I) and interleukin-2 (II). Recombinant II [1-de-L-Ala-125-L-Ser-interleukin-2 (human)] obtained from Escherichia coli was formulated at a concn. of 0.3 mg/mL with 50 mg/mL *mannitol* . Recombinant I [17-L-Ser- *interferon* -. *beta* . (human)] was formulated at a concn. of 25 mg/mL with 12.5 mg/mL serum *albumin* and 12.5 mg/mL dextrose. Patients were simultaneously administered I and II 3 times weekly for a min. time of 1 mo; in most patients who demonstrated LAK activity evidence of antitumor activity was also seen.

L58 ANSWER 9 OF 9 CA COPYRIGHT 1997 ACS DUPLICATE 3
AN 99:181455 CA
TI Stable *interferon* . *beta* . compositions containing poly(vinylpyrrolidone)
IN Symbalista, Samuel
PA Inter-Yeda Ltd., Israel
SO Eur. Pat. Appl., 13 pp.
CODEN: EPXXDW
PI EP 89245 A2 830921
DS R: AT, BE, CH, DE, FR, GB, IT, LI, NL, SE
AI EP 83-301470 830316
PRAI IL 82-65277 820317
DT Patent
LA English
AB Human fibroblast *interferon* . *beta* . solns. are stabilized by poly(vinylpyrrolidone) (PVP) [9003-39-8] (0.5-5%) for clin. use. The interferon compn. does not lose its activity on storage. Thus, a pH 3.5 aq. acetate buffer was prepd. by dissolving HOAc and NaOAc in water. The inner surface of a dialysis bug was wetted with sufficient conc. human serum *albumin* to give *interferon* . *beta* . soln. with a sp. activity of 107 IU/mg protein. The soln. was dialyzed against the acetate buffer at 4.degree. for 48 h and the dialyzed *interferon* . *beta* . soln. was mixed with 0.5% wt./vol. *mannitol* and 2% wt./vol. PVP prior or following filtration through a sterile filter. Two mL each of the resulting soln. was dispensed into glass vials, and the solns. lyophilized and the vials were sealed and stored at 4.degree.. The final compn. contained/vial NaOAc 0.4, NaCl 1.8, human serum *albumin* 40.0, *mannitol* 10.0, and PVP 40 mg and interferon 1.0 .times. 106 IU. PVP of different mol. wts. (10,000-700,000) at 2-4% concns. stabilized the *interferon* . *beta* ., as demonstrated by storage stability tests.

=> log y
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